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# ANNALS OF INTERNAL MEDICINE

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## CRANIAL ARTERITIS: A CRITICAL EVALUATION OF THE SYNDROME OF "TEMPORAL ARTERITIS" WITH REPORT OF A CASE \*

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"TEMPORAL arteritis" is a rare, febrile, self-limited disease of variable duration and unknown etiology. It afflicts the aged of both sexes and is characterized by painful inflammation of the temporal arteries and the general systemic signs and symptoms of malaise, weight loss, anorexia, fever, sweating, and weakness. Since 1932, when Horton, Magath, and Brown first described this symptom complex as an entity, 20 case reports have appeared in the literature. The identity of this disease has been challenged by several authors, notably by Jennings, who states that temporal arteritis cannot be differentiated from periarteritis nodosa. Indeed, in the New York Hospital, temporal arteritis has been noted in a proved case of periarteritis nodosa.

It is the purpose of this paper to attempt an evaluation of "temporal arteritis" as a clinical and pathological entity, with special reference to its differentiation from other forms of arteritis. The following description of temporal arteritis, based on a study of the 20 published case reports and a detailed investigation of our own case, has led us to a broader conception of the nature of this malady.

*Incidence.* The rarity of this disorder is indicated by the paucity of case reports (20) in the 13 years since its first description.

The age incidence is 55 to 80; the incidence is greater in women, being about 3:1, and the disease has been noted only in those of the white race residing in the United States of America and England. No seasonal predilection has been observed.

*Symptomatology.* The symptomatology of this disease may be divided into the non-specific complaints of generalized, systemic nature, and those

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complaints directly attributable to inflammation and distention of the temporal and other arteries.

*Non-Specific Complaints.* In every case there have been signs and symptoms which cannot be plausibly related to sterile inflammation of the temporal arteries alone, and which are more suggestive of chronic or sub-acute infection.

Prevalent symptoms and signs are: weight loss, anorexia, general malaise, fever, sweating, and weakness. The weight loss may be profound (30 pounds), and the patient emaciated.<sup>8</sup> This is probably secondary to anorexia, which, although in certain cases a concomitant of the excruciating pain and headache, may antedate the onset of pain, as in our case. Sweating is a common symptom, and in our patient occurred during the stage of acute arterial inflammation.

Inconstant, low-grade fever unassociated with shaking chills is recorded in 70 per cent of the cases. In only two cases is the absence of fever specifically mentioned,<sup>4, 13</sup> and in the descriptions of four cases no reference is made to body temperature. The average temperature is 37.8° C., although recordings as high as 39.5° C. have been made.<sup>1</sup>

Other complaints of a non-specific nature are weakness, lassitude, malaise and "grippy feelings" and fatigue (occasionally to the point of prostration).<sup>8</sup> Nausea, vomiting, and dizziness may occur,<sup>9, 12</sup> but it is debatable whether these symptoms are manifestations of a sepsis, or specific reaction to involvement of the cerebral arteries, as postulated by Bowers.<sup>7</sup>

*Specific Symptoms* (probably referable to inflammation of the temporal and other arteries).

(1) *Pain.* All patients with "temporal arteritis" have headache. It is severe, throbbing in nature, steady, and associated with hyperalgesia of the scalp. Fifty per cent of the patients suffer pain on mastication,<sup>14</sup> and in some this is the initial symptom. Facial swelling and redness of the skin overlying the temporal arteries, with the addition of a burning component of pain, are usually noted after the onset of headache. Immediate relief from pain and headache may follow biopsy of the inflamed temporal artery<sup>7</sup> and it is presumed that this follows the interruption of the afferents for pain about the vessel. Exacerbation of pain and arterial inflammation followed the extraction of three infected teeth in a case reported by Profant.<sup>14</sup>

Prior to the onset of the full-blown picture of temporal arteritis, there is often pain in the teeth,<sup>1</sup> ear,<sup>3</sup> jaw, zygoma,<sup>3, 6, 13</sup> nuchal region and occiput.<sup>7</sup> This symptom suggests primary involvement of other branches of the external carotid artery, notably the external and internal maxillary arteries.

The fact that in one patient pain has been noted along the course of the brachial and radial arteries and the arteries of the hands prior to the onset of temporal arteritis<sup>9</sup> suggests the possible polyarteritic nature of at least some cases of this disease. This is further implied by Jennings' description of a patient who suffered from pains in the thighs, knees, and ankles for nine

months prior to the onset of headache.<sup>4</sup> In the former case, however, the follow-up reported was inadequate to rule out periarteritis nodosa.

(2) *Ocular Symptoms.* The presenting complaint may be of ocular symptoms.<sup>8</sup> Indeed, it has become evident that more than a third of patients with temporal arteritis are threatened with partial or even complete loss of vision.<sup>4, 6, 9, 12, 13</sup> Diplopia and photophobia have been noted<sup>4, 6</sup>; ophthalmoscopic evidence of occlusion of the central retinal artery has been apparent in some cases,<sup>4, 12</sup> and one case with complete loss of vision has been reported.<sup>18</sup>

(3) *Cerebral Symptoms.* Four patients have presented signs suggestive of cerebral damage and encephalitis<sup>5, 8, 10, 7</sup> during the acute stage of the illness. Sprague and McKenzie report that their patient was considered by his intimates never to have recovered fully from his symptoms of lethargy and mental retardation. Mental sluggishness, dizziness, vomiting, dysarthria, delirium, and even coma have been described, and abnormalities in the spinal fluid colloidal gold curve were found by Schaefer and Sanders<sup>10</sup> in a patient with delirium and headache. In our patient acknowledged irritability and retardation of thought were noted.

(4) *Other Symptoms.* Although the average age incidence was 67, it is notable that in only two cases was the symptom of chest pain mentioned. Of these, one was our patient, and he claimed no increase in his rare anginal pains which had occurred intermittently during the past three years.

Symptoms and signs referable to the smaller visceral arteries commonly involved in periarteritis nodosa were not evident, and the hypertension frequently encountered in the latter<sup>15</sup> was infrequently encountered in cases of temporal arteritis.

*Course.* "Temporal arteritis" is a self-limited disease of one to 20 months' duration which may be attended by relapse,<sup>1, 18</sup> but which is apparently non-fatal. With the exception of visual defects secondary to arterial occlusion recovery is apparently complete and accompanied by returning pulsation in temporal arteries which completely lose all evidence of inflammation or nodularity.<sup>14</sup> The course of the illness seems to be unaffected by treatment, although relief has followed arterial biopsy in a few cases.<sup>7, 9</sup>

In patients who suffered visual loss, recovery of this function did not occur, and as noted above, at least one patient may have incurred permanent cerebral damage during the acute illness.

*Laboratory.* Tests of renal and liver function were non-contributory. A constant finding was a moderate leukocytosis ranging from 7,500 to 14,500 and averaging 12,000 to 13,000. Eosinophilia was absent.

*Bacteriology.* Because this disease is characterized by many features of a low-grade infection, and because its natural history suggests a spread of infection from the mouth or paranasal sinuses, there has been a search for a bacterial agent. Horton, Magath, and Brown isolated an actinomyces from the arterial walls of two of their cases, but this organism was considered to be a contaminant.

Dick and Freeman<sup>6</sup> isolated *Streptococcus viridans* from a biopsied artery, and cultured B-hemolytic streptococcus from the patient's throat. Bowers<sup>7</sup> cultured Gram positive cocci from his biopsied specimen, and MacDonald and Moser<sup>2</sup> obtained *Staphylococcus aureus* from the artery. In the latter case<sup>2</sup> *Streptococcus viridans* was isolated from a periapical tooth abscess.

Thus, it is evident that there is no constant bacteriological finding, and none of the postulates of Koch has been fulfilled. All blood cultures have been sterile, and routine agglutinations have been negative.

*Pathology.* Much of the dispute concerning the identity of "temporal arteritis" as a syndrome distinct from periarteritis nodosa stems from the similarity of the histological sections of the vessels involved in the two diseases. In both, the process is a panarteritis which involves all three arterial coats.

Typically, periarteritis nodosa (polyarteritis nodosa) affects only the smaller arteries (3-4 mm.) which supply the viscera, muscles, joints and subcutaneous structures, although in at least one case (studied in this clinic) the temporal artery was involved, and revealed at biopsy typical periarteritis nodosa. Grossly, the arteries are characterized by nodular, periarterial swellings which may be palpated during life.

In "temporal arteritis" the involved arteries are grossly seen as tortuous, swollen, nodular vessels with or without pulsation, with cellulitis of contiguous tissue. Evidence points to the involvement in some patients of the central artery of the retina, the occipital, radial, facial, carotid,<sup>9</sup> brachial, and cerebral arteries. In our patient there was radiographic evidence of calcification of the internal carotid and calcification with possible aneurysmal dilatation of the basilar artery.

Biopsies of temporal arteries have been performed in 13 of the 20 cases reported, but no patient with the disease has come to autopsy. Microscopic examination reveals a pan-arteritis which cannot be readily distinguished from that of periarteritis nodosa. The typical section reveals hypertrophy of the intima, medial necrosis associated with the formation of granulomatous tissue and the presence of foreign body giant cells, periarterial cellular infiltration, and thrombus formation. It is pointed out by Horton et al.<sup>8</sup> that unlike periarteritis nodosa, the microscopic picture of "temporal arteritis" reveals the frequent presence of giant cells but no aneurysmal dilatations. Eosinophilic invasion of the artery in "temporal arteritis" appears to be rare, although it is reported by Bowers<sup>7</sup> and is a prominent feature of our own sections. The presence of giant cells has suggested a tuberculous etiology, but no tubercles have been seen and no acid fast bacilli have been demonstrated.

The following case notes illustrate: (1) the progression of the "arteritis" as indicated by the distribution of pain from the lower half of the head to the temporal region; (2) the multiplicity of the arterial branches involved; (3) the non-specificity of the cellular reaction, suggesting non-specificity of

etiology. It is especially notable that this case while conforming clinically to the accepted picture of "temporal arteritis" displayed in the excised artery histopathological changes which have been encountered in only one other case in the literature.

#### CASE REPORT

A 68 year old married white male architect presented himself in November, 1944 (see figure 1) with a severe headache associated with prominent temporal arteries



FIG. 1.

and tenderness of the skin and soft tissue in both temples and across the forehead. Two months previously (September) his appetite had become poor, he began to tire easily, and found that he had lost six pounds in weight. Shortly afterward he had a sustained pain in his left lower jaw. He noted, coincidentally, that he had a small ulcer on the gum which was irritated by his denture. However, when he removed his lower plate, the pain continued. In a few days the pain had extended to his left ear, and some days later the left temporal arteries became swollen and painful.

In three weeks from the onset of the first symptoms, he had an aching pain in both temples, across his forehead, over both left and right zygomatic regions and bilaterally in the walls of the buccal cavity. His cheeks and temples appeared slightly swollen and his masseter muscles ached when he opened his mouth. The skin over

his cheeks, temples and forehead was hyperalgesic. He said, "It felt as if I had a sunburn, and I couldn't bear to rub my fingers over it. Just to touch the hair of my temples was painful." The patient described the pain as being of two varieties, a superficial burning pain (like sunburn) and a deep aching pain, both of high intensity.

He had a pain of low intensity in his chest on exertion, his temperature was elevated, and he felt languid, lacked energy, and had no appetite. He had occasional night sweats. He could recall no headaches previous to his present illness.

Twenty years previously he had had bronchitis followed by a chronic cough, and eight years previously a "streptococcus infection" of the throat, and subsequent tonsillectomy and extraction of all of his upper teeth. With the exception of these two illnesses his general health had been good. For the past three years he had complained of substernal pain on exertion, and dyspnea on climbing 1-2 flights. These latter symptoms had not increased since the onset of the present illness.

On admission to the hospital the patient looked old and as though he had been ill for some time. The temporal arteries were large, distended, tortuous and nodular, being more prominent on the left than on the right. They were found to pulsate, and the walls were tender, thickened and firm, but compressible. They were palpable from the temporomandibular joint to the vertex of the skull, bilaterally (see illustration).

There was a tremor of the tongue and outstretched hands, and upward gaze was incomplete. Ankle jerks were absent and there was diminished vibration sense in the lower extremities. The pedal pulses were absent. Examination of the eye grounds revealed a small white patch of exudate adjacent to the superior nasal branch of the left retinal artery. Radial arteries were palpable and firm. The radial pulse was regular and the rate was 80. The heart sounds were not remarkable and the heart was not enlarged. The blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The patient's temperature was elevated ( $38^{\circ}$  C.), and his white blood cell count was 13,600. The sputum was negative for acid fast bacilli. Extensive laboratory examinations of blood, urine, stool, spinal fluid, and roentgenograms of the teeth and sinuses were non-contributory. Other roentgenograms revealed a healed minimal fibroproductive tuberculosis in the subclavicular area of the right lung, calcification of the internal carotid and basilar arteries, and arteriosclerosis of the vessels of both lower extremities. Just posterior to the dorsum sellae there was stereoscopically a spherical area of calcification which suggested an aneurysmal dilatation of the basilar artery or of the Circle of Willis. There was no roentgenographic evidence of sclerotic changes in the vascular bed of the arms. The electrocardiogram showed left axis deviation, a QRS time at upper limit of normal, and a prolonged P-R interval.

During the first six days after admission to the hospital the intensity of the pain in the head diminished rapidly. It was noted that the burning component ended before the deep aching. During the next 12 days in the hospital, the patient was almost free of pain, although the symptoms of lassitude, anorexia and weakness persisted, and night sweats occurred on several occasions. Both the pulsations which were visible in the temporal arteries and the tenderness which was present on admission disappeared. At the time of discharge from the hospital these large, distended, tortuous vessels were still firm and thickened, and pulsations could not be felt. There was no edema nor gross inflammatory reaction of adjacent tissues.

A section about 2 cm. in length of the parietal branch of the right superficial temporal artery was excised. Microscopic examination revealed the walls of the vessel to be the site of very marked inflammation throughout, with diffuse infiltration by lymphocytes and occasional polymorphonuclear leukocytes. There was as well periarteritis of the vasa vasorum. There was edema of the muscularis. The lesion was one of subacute inflammation which was characterized by innumerable lympho-

cytes, eosinophiles and fibroblastic proliferation. Giant cells were not found. The adjective "nodosa" was not applicable. However, all the elements of the vessels were uniformly and diffusely inflamed, as in a panarteritis.

The patient returned to his home on November 18, 1944. He remained free of pain and tenderness in the temporal regions, and the swelling of the arteries gradually diminished and ultimately disappeared completely. Although he appeared to have regained his health, on December 10 he had a coronary occlusion which was followed by heart failure. A second coronary occlusion on January 30 led to his death on February 1, 1945.

*Comment.* The patient here described, like others mentioned before, had initial non-specific symptoms of anorexia, weight loss, and fatigability, and at this time presented no evidence of active inflammation of the temporal arteries, i.e., headache, or painful swelling of these vessels.

Of major interest is the fact that the patient's first painful symptoms were not in the vicinity of the temporal artery, but rather in the lower jaw, an area supplied by branches of the external maxillary artery. This seems of special import in view of the fact that in at least half of the other patients with "temporal arteritis" the initial, painful, local symptoms occur in regions remote from the temporal artery. Because of the later obvious inflammation of the temporal artery and the temporal regions in these cases, it is reasonable to assume that the preceding jaw pain and stiffness, mouth stiffness, nuchal pain and tenderness, facial ache, occipital pain, and visual loss were secondary to a like acute inflammation in other branches of the carotid arteries supplying these regions. Tenderness over the carotid artery itself has been noted in another case.<sup>9</sup>

In this case, as in others, search for a bacterial agent by agglutination and blood cultures proved fruitless, although a leukocytosis, elevated sedimentation rate, fever and sweats were evidence for the infectious nature of the process.

The electrocardiogram in our patient (soon to die of coronary occlusion) on two occasions revealed prolongation of the P-R interval, and Q-R-S times at the upper limits of normal. Other evidence of a generalized arterial inflammation, as seen in rheumatic arteritis and periarteritis nodosa, was carefully sought for, but not elicited. Blood pressure was normal, renal function tests were normal, eosinophilia of the peripheral blood was not noted, and abdominal and muscular pains in the extremities were not evident. No evidence of heart failure was ever apparent.

The subsidence of temporal arterial swelling and the general improvement in the patient's condition prior to his coronary accident may justify the conclusion that his coronary artery disease was a coincidental occurrence in an elderly man. It may be that the coronary occlusion was related in no way to the acute inflammatory process involving the arteries of his head.

*Concept of Etiology and Pathogenesis.* The majority of patients suffering from "temporal arteritis" present evidence, by sign and symptom, of a generalized, debilitating, subacute disease. To this extent they super-

ficially resemble generalized, inflammatory diseases of blood vessels such as periarteritis and disseminated lupus. With rare exception, however, these diseases are progressive and unremitting processes which terminate fatally. It can be said with reasonable certainty that all cases of "temporal arteritis" have shown complete recovery despite the advanced ages of the persons affected, and that any residual damage is secondary to thrombosis of the branches of the carotid, and not the result of continued, active inflammation of a polyarteritic nature. Furthermore, in patients with "temporal arteritis" there is no impairment in visceral circulatory function such as has been noted in periarteritis nodosa.

It seems reasonable to postulate that the systemic symptoms of "temporal arteritis" are those of a low grade, self-limited infectious process in an elderly person of lowered resistance. There is some evidence of preceding or concomitant infection in the cases reported in the literature. In 11 of the 21 cases studied, there were signs, symptoms or other evidence of preceding or concomitant infection in the head. Seven cases presented evidence of periapical tooth or other mouth infection. One patient recovered soon after tooth extraction,<sup>3</sup> whereas another showed a recrudescence of symptoms following removal of three diseased teeth.<sup>14</sup> The patient presented in our case report had noted an ulceration of the gum at the onset of the pain in his jaw, and preceding the "temporal arteritis." This was presumably a deep infection because it was not relieved by removal of his denture. In two patients large tender cervical lymph nodes were noted during the period of arteritis<sup>6, 11</sup>; in another a "sore throat" believed severe enough to warrant treatment with "prontosil" was described. Roentgenological evidence of pansinusitis was discovered in still another patient.

It is presumable that "temporal arteritis" may be an allergic reaction of the arteries of the head to the bacterial products of mouth infection. Against an allergic origin, however, are: (1) the rarity of eosinophilia, (2) the advanced age of the patients affected, and (3) the localized distribution of the arteritis.

The relatively high incidence of concomitant or preceding mouth infection plus the fact that the initial pain may occur in the teeth or jaw suggests the possibility of involvement of neighboring arteriosclerotic arteries by direct extension of local infection.

Because the temporal artery is the most superficial and prominent artery of the head, its involvement in an acute inflammatory process is easily detected. It is for this reason that the name "temporal arteritis" was appended to a disease characterized by inflammation of many other branches of the common carotid artery. The facts presented make untenable the view that "temporal arteritis" is solely a disease of the temporal artery. Therefore, the name "cranial arteritis" is proposed as more appropriate for this clinical syndrome.

## SUMMARY AND CONCLUSIONS

1. The syndrome heretofore designated as "temporal arteritis" is a well-defined symptom complex occurring in aged people of the white race.

2. All but one of the patients studied presented signs and symptoms generally associated with infection, namely, anorexia, prostration, fever, sweats, weight loss, and leukocytosis; and locally, over the artery, there was heat, swelling, tenderness, redness and pain.

3. The distribution of pain and tenderness is indicative of preceding or concurrent inflammation of the arteries of the lower half of the head. In half of the patients pain over the distribution of these arteries was primary.

4. In more than half of the patients studied there was evidence of preceding or concomitant infection in the head, suggesting the possibility of spread of this infection by contiguity along the walls of branches of the external carotid artery.

5. Differentiation of "temporal arteritis" from periarteritis nodosa cannot be made from the study of histopathological sections of the diseased arteries. Although in many cases of "temporal arteritis" giant cells are found, in some eosinophilic infiltration in the absence of giant cells has occurred. Thus, there is no specificity of cellular reaction.

6. The name "temporal arteritis" is misleading, since it is probable that the disease involves other arteries of the head. Therefore, for the syndrome heretofore known as "temporal arteritis," the term "cranial arteritis" is proposed as a definitive and inclusive descriptive title.

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## POLYARTERITIS NODOSA: REPORT OF 11 CASES WITH REVIEW OF RECENT LITERATURE\*

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PERIARTERITIS nodosa is an obliterative, inflammatory, vascular disease involving the small arteries and arterioles. Periarthritis nodosa is an inadequate descriptive term since all coats of the vessel are involved, and since nodules may or may not be present. Polyarteritis is a more exact name. Polyarteritis is a rare condition, 350 cases having been reported up to 1942.<sup>41</sup> Males are involved more frequently than females, in contrast to acute disseminated lupus erythematosus. It may occur at any age, having been reported from ages 1 to 79. Fifty per cent of the patients are in the fourth and fifth decades.<sup>8</sup> Reports of cures are infrequent.<sup>17, 22, 32</sup> The mortality may be as high as 90-95 per cent, although with increasing recognition of mild or atypical cases, these figures will undoubtedly be considerably lower.

*Etiology.* The etiology is unknown. Rich and his coworkers<sup>38a</sup> have recently reproduced the condition in rabbits by sensitization to serum and to sulfonamides. They had previously noted the condition in patients who had received serum and sulfonamides or sulfonamides alone.<sup>38b</sup> Previous workers<sup>28, 43</sup> reproduced lesions by injection of horse serum into rabbits and others<sup>20</sup> by injection of macerated material from human cases. In the light of Rich's work it is probable that these lesions were of an allergic nature. Eason et al.<sup>11</sup> reported a case which followed the administration of scarlatinal serum to a patient with acute rheumatic fever, but did not feel that the serum was responsible. Clark and Kaplan<sup>9</sup> studied four patients at autopsy who had experienced serum sickness following the administration of serum for pneumonia, and two of them showed lesions of polyarteritis nodosa; however, they concluded that distinctive lesions do not follow serum disease. Cohen<sup>10</sup> has emphasized an irreversible allergic reaction in the vessel wall. Many workers<sup>14, 16, 31</sup> have commented on the frequency of association of polyarteritis nodosa and rheumatic fever or rheumatic heart disease. Selye<sup>38</sup> has produced arthritis similar to rheumatic fever and lesions similar to polyarteritis nodosa by the administration of desoxycorticosterone acetate to rats, suggesting a possible hormonal reaction. In the past, syphilis, streptococcal infections, toxic reactions,<sup>21</sup> and a filterable virus<sup>20</sup> have been mentioned as possible etiologic factors, but the evidence to support such theories is insufficient. It is probable that the etiology is diverse; perhaps it will be found that sensitization to serums, drugs, and infections may all play a part in its production.

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*Pathology.* The pathologic lesions are quite variable, and it is obvious that this will depend upon the vessels involved in any given case. The tissues involved in the order of frequency are kidneys (80 per cent), heart (60 per cent), liver (47 per cent), spleen, lungs, mesentery, peripheral nerves, skin and brain. It has impressed this author how often one sees involvement of the testicular arteries in addition.

The lesions are generally distributed in a patchy manner. One frequently finds the vessel wall to be normal in an area adjacent to an involved segment.

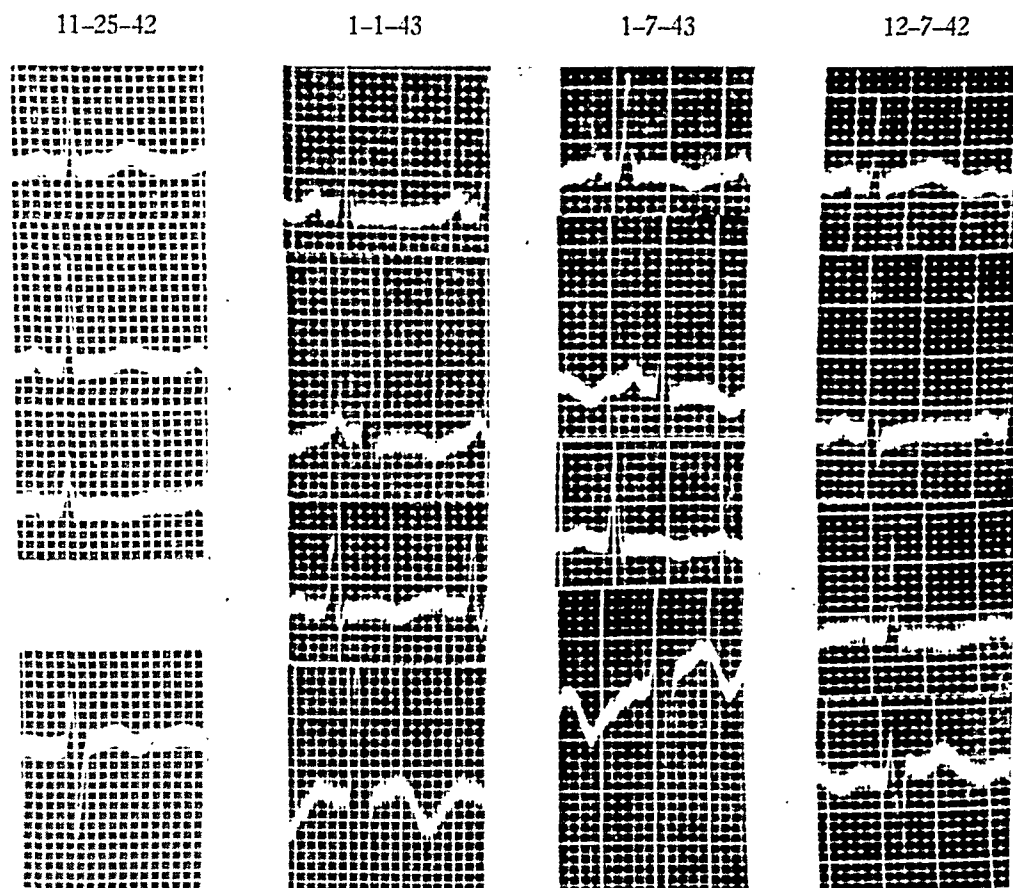


FIG. 1. Case 6. Note inversion of T, 11-25-42. Subsequently digitalized. T-waves became progressively inverted in all leads with slight depression of ST<sub>2</sub>.

Arkin<sup>2</sup> arbitrarily divides the pathologic lesions into four stages: (1) degenerative; (2) acute inflammatory; (3) granulation; (4) healed. In the first stage there is hyaline degeneration of the media. In the second stage the coats become infiltrated with polymorphonuclears, eosinophiles, lymphocytes, and plasma cells. In the third stage, there is a fibroblastic proliferation with partial or total occlusion of the lumen. In the fourth stage, the lumen is greatly reduced or obliterated, and the wall is replaced by scar tissue and periarterial fibrosis. Any or all stages may be present at any given time. One not uncommonly finds the healed stage alone at autopsy.<sup>5</sup> The healed

lesions have no features which distinguish them from other forms of arteritis.<sup>18</sup> The healed stage may occur only a short while after symptoms of activity have been noted, and leads one to suspect that the change from one stage to another may be quite rapid. The frequency with which subcutaneous nodules appear and disappear over a period of a few days lends further evidence for this view. Biopsy should be performed immediately on suspected nodules, for all too often the opportunity of pathologic confirmation is lost when a few days are allowed to elapse.

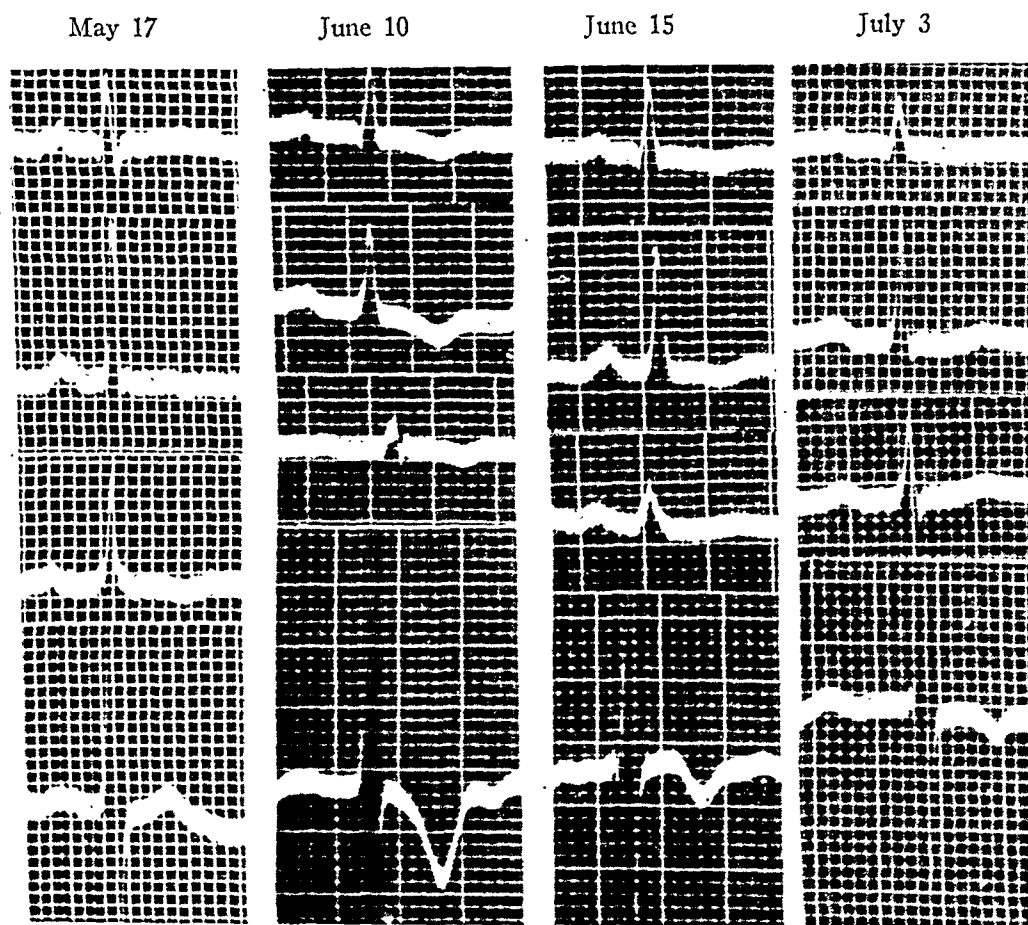


FIG. 2. Case 8. Note low  $T_1$ , diphasic  $T_2$  and  $T_3$  on May 17. Subsequently digitalized. T-waves became inverted in all leads with development of incomplete AV block and slight depression of ST in Leads II and IV.

All coats of the vessels are involved, although the primary involvement is thought by some observers to be in the media. As a result of the obliterative process and proliferation of the intima, thrombosis with infarction and areas of fibrosis may be noted in the organs involved. Aneurysmal dilatation and nodule formation along the arteries are common, and may give rise to the "peas in the pod" appearance, particularly in the coronary arteries. In rare instances the veins may be involved. Gross examination may at times show no abnormalities, and the diagnosis necessarily rests upon the microscopic

examination. Even so, the lesions may be missed if the condition is not suspected. Grant has stressed the importance of repeated serial sections; the diagnosis in one case could not be established until repeated sections were made.<sup>18</sup> The relation of polyarteritis to acute disseminated lupus erythematosus is puzzling and has been commented upon by a number of observers.<sup>3, 40</sup> Cases of polyarteritis clinically have shown the lesions of lupus at autopsy, and on the contrary, patients with the clinical picture of lupus

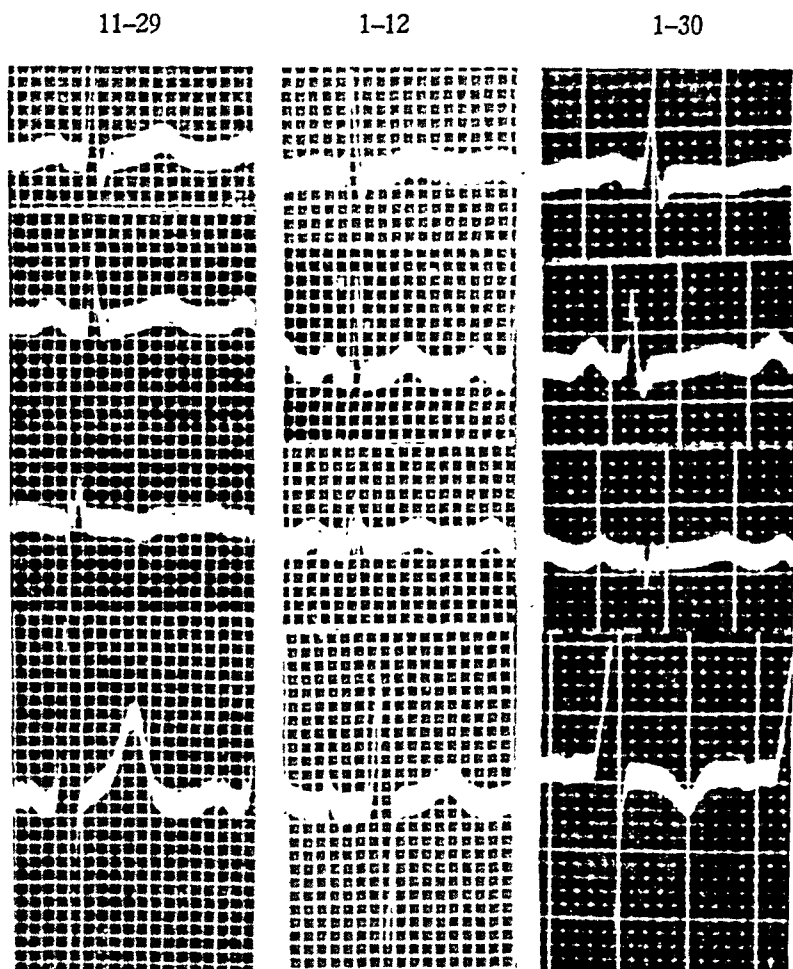


FIG. 3. Case 5. Note inversion of  $T_1$  and  $T_4$  with flattening of  $T_2$  and  $T_3$  on 1-30. No digitalis.

have shown polyarteritis at autopsy. Klemperer et al.<sup>24</sup> have commented on diffuse collagen disease, particularly in relation to periarteritis, disseminated lupus, rheumatic fever and scleroderma.

*Symptoms.* The symptomatology may be extremely variable and depends upon the tissues involved. It is common for several systems to be affected. Emerson et al.<sup>12</sup> have emphasized the changing character of the symptoms. The symptoms of 177 cases reported in the English literature are tabulated in table 1. Various syndromes such as chlorotic marasmus,

polyneuritis, or polymyositis and severe gastrointestinal symptoms such as described by Meyer,<sup>30</sup> or asthma, peripheral neuritis and eosinophilia as described by Rackemann,<sup>34</sup> or nephritis, anemia, and peripheral neuritis as described by Brinkman<sup>7</sup> have been reported. Spiegel<sup>40</sup> commented on the

TABLE I

Symptoms of Polyarteritis Nodosa—177 cases (modified after Harris, W. A., Lynch, G. W., and O'Hare, J. P.<sup>10</sup>)

Fever .....	81%
Leukocytosis .....	73%
Albuminuria .....	65%
Abdominal pain .....	56%
Hypertension .....	53%
Edema .....	49%
Neuritis .....	49%
Hematuria .....	48%
Rapid onset .....	45%
Weakness .....	45%
Loss of weight .....	44%
Dyspnea .....	40%
Cough .....	36%
Emaciation .....	34%
Sensory involvement .....	34%
Arthritis .....	34%
Vomiting .....	33%
Eosinophilia (4% plus) .....	33%
Purpura or petechiae .....	27%
Headache .....	26%
Visual disturbances .....	23%
Nodules .....	23%
Nausea .....	21%
History of allergy .....	21%
Atrophy .....	20%
Cyanosis .....	20%
Pain in chest on pressure .....	17%
Icterus .....	12%
Convulsions .....	11%
Positive serologic reaction .....	8%
Vertigo .....	5%
Other skin eruption in absence of purpura .....	4%

#### Other Symptoms in 76 Cases

Anemia .....	48%
Tachycardia .....	48%
Central nervous system involvement .....	26%
Muscle soreness .....	26%
Coma .....	21%
Uremia .....	13%
Hematemesis or bloody stools .....	18%
Adenopathy .....	11%
Chills .....	8%
Diarrhea .....	6%
Hemoptysis .....	1%

disproportion between the number and intensity of symptoms, and the disease assumed to be their cause. Fever, loss of weight, weakness, anorexia, and tachycardia are common constitutional manifestations. In the later stages of the disease, emaciation and cachexia may be striking. The disease usually extends over a period of many months, and at times years. Reports of cures

following the administration of sulfonamides or other drugs should be viewed critically, since spontaneous remission for long periods of time or even spontaneous cures have been noted.

Renal involvement may be indicated by albuminuria which occurs in 65 per cent of the cases. Painless hematuria is at times noted, and Boyd<sup>6a</sup> has suggested that certain cases of so-called essential hematuria may fall into this group. Pain in the flanks may accompany hematuria and usually indicates infarction or perirenal hemorrhage. Collapse and death due to ruptured aneurysms of the interlobular arteries with the formation of large perirenal hematomata was noted in 18 cases by Boyd.<sup>6a</sup> The shadow cast by such a mass on roentgen-ray has been mistaken for renal tumor.<sup>37</sup> Acute glomerulonephritis is not uncommonly simulated. In time, symptoms of renal insufficiency may occur and uremia is a frequent terminal event. The arteries of the testicles and epididymis are not uncommonly involved and may give rise to localized pain and swelling in this region. Orchitis due to infarction is a rare complication. Scrotal pain has been reported.<sup>19</sup>

Symptoms of coronary insufficiency with or without associated heart failure are frequent. Myocardial infarction is rare, probably owing to the slow rate of occlusion, which allows the formation of adequate collateral circulation; however, it has been recorded.<sup>18</sup> Hypertension is common and occurred in 53 per cent of 177 cases. It is of particular significance when it appears during the course of illness in a suspected case. The appearance of hypertension is frequently a late phenomenon, and thus, its diagnostic value in early cases is limited. Cardiac enlargement may occur in the absence of hypertension as a result of chronic coronary insufficiency. Rarely localized nodular thickenings may be palpated along small superficial arteries. The temporal arteries may exhibit such involvement, but more commonly this manifestation is unassociated with periarteritis nodosa. The vascular changes in the retinal vessels are generally secondary to hypertension. Thrombosis of the central retinal artery,<sup>4</sup> transient amaurosis and bilateral optic atrophy are among conditions reported.<sup>6b</sup> Pericarditis and pericardial tamponade due to rupture of an aneurysm of a coronary artery have been reported.<sup>42</sup> The endocardium may be involved by nodule formation or inflammatory thickening.<sup>21, 45</sup>

In a study of 200 cases, Ketron<sup>23</sup> found involvement of the skin in 25 per cent. The most characteristic lesion takes the form of subcutaneous nodules. These occur singly or in crops, are usually painless, and quite transient. Rarely they may pulsate.<sup>47</sup> Nodules were noted in 23 per cent of 177 cases. The most common skin lesion is petechia or purpura. Vesicles, urticaria, livedo reticularis, erythema and scarlatiniform eruptions have been reported. Ulceration of the skin due to thrombosis of the cutaneous arteries may occur.<sup>28</sup>

Neuritis is not uncommon and follows involvement of the nutrient arteries of the nerves in which thrombosis and infarction may or may not take place. With partial occlusion of the arteries, ischemia with subsequent

paresthesias may occur. These disappear with improvement of the circulation. Involvement of single nerves in the extremities is most common. More than one nerve may be involved, but the involvement is asymmetrical, since nerves are affected individually at different times.<sup>44</sup> Foot drop, wrist drop, motor weakness, sensory changes and paresthesias may result. Central nervous system manifestations were noted by Foster and Malamud<sup>15</sup> in 65 (20 per cent) of 300 cases. Among the most common manifestations were convulsions, meningeal irritation, organic brain syndrome, hemiplegia, sluggish pupil, anisocoria, cerebellar signs, Jacksonian convulsions, facial palsy and subarachnoid hemorrhage.

Muscle pain and soreness are common. The symptoms may simulate trichiniasis.<sup>35</sup> Joint symptoms are frequent, and may vary from arthralgia to acutely swollen joints. Migratory polyarthritis may occur.

Abdominal pain may be a prominent symptom. It is usually poorly localized, but is perhaps more common in the epigastrium. Boyd<sup>6c</sup> reported abdominal pain in 50 per cent of 168 patients, and in 25 per cent the pain was epigastric. The pain may simulate acute appendicitis, typhoid fever, cholecystitis, gastric ulcer, gastric carcinoma, acute pancreatitis, tuberculous enteritis and carcinoma of the colon. The mesenteric arteries are a favorite site of involvement. Thrombosis may result in infarction of the bowel wall giving pain and occult blood in the stools. Ulcerative enterocolitis with or without bloody diarrhea may result. Peritonitis may follow rupture of the bowel wall.<sup>14, 27, 33</sup> Felsen<sup>13</sup> made a diagnosis by proctoscopic examination, which revealed the vessels as persistent linear red streaks. Laparotomy is frequently performed because of obscure abdominal pain. Seven of Spiegel's<sup>40</sup> 17 cases were submitted to laparotomy, and in five a preoperative diagnosis of acute appendicitis was made. Singer<sup>39</sup> reported two cases with abdominal complaints, one of whom underwent cholecystectomy and the other missed operation because of unexplained delirium. Allen<sup>1</sup> reported a case with abdominal pain and boardlike stiffness of the abdomen in which operation was performed for perforating ulcer. There were extensive adhesions between the omentum and abdominal wall. Subsequent autopsy revealed periarteritis nodosa. Emerson<sup>12</sup> reported a case with a pulsating mass and systolic murmur in the right upper quadrant which was due to an aneurysm of the right pancreaticoduodenal artery with the formation of a retroperitoneal hematoma.

The liver is at times enlarged and jaundice may occur.<sup>31</sup> Involvement of the cystic artery may give rise to symptoms of acute cholecystitis. Middleton and McCarter<sup>31</sup> reported a case in which diabetes mellitus developed during the course of illness and autopsy revealed extensive involvement of the pancreas and its arteries. On rare occasions the spleen may be palpable. The superficial nodes are at times enlarged.

Cough, pain in the chest, and asthma are the most common pulmonary complaints. Dyspnea is usually secondary to asthma or left heart failure. The most common pathologic findings are whitish nodules along the small



pulmonary arteries, particularly in the peribronchial region near the hilum.<sup>25, 45</sup> Areas of fibrosis secondary to small areas of infarction may occur and at times can be detected in roentgenograms of the chest. These findings have at times given rise to an erroneous diagnosis of tuberculosis.<sup>26</sup> The association of asthma and polyarteritis nodosa is of some interest, particularly in view of Rich's<sup>30a, b</sup> recent work on sensitivity. Rackemann and Greene<sup>34</sup> reported eight cases with asthma and collected 27 others from the literature. Any asthmatic with marked eosinophilia should be a suspect, and Rackemann states that asthma, numbness in the extremities and eosinophilia of more than 25 per cent indicate polyarteritis nodosa. This is particularly true in females. A careful history of allergy should be sought. This has not been a striking clinical feature, although 21 per cent of 177 cases gave such a history. It may be that this will be found more commonly if a thorough search is performed. A history of intolerance to drugs, particularly sulfonamides, should be sought. McCall and Pennock<sup>29</sup> were unable to correlate the vascular lesions with preceding sulfonamide therapy in a series of 10 cases.

*Laboratory Findings.* Leukocytosis with a mild shift to the left is a common finding in the active stages of the disease. Repeated search for eosinophilia should be performed, as it is an inconstant finding, and is probably related to periods of fresh activity. It is probable that the figure of 33 per cent is too small and that repeated counts would give a higher figure. Cases which have shown no eosinophilia may suddenly show a sharp rise at some time during the course of illness. Extremely high eosinophile counts may at times be noted; Rackemann<sup>34</sup> reported a case with 84 per cent eosinophiles. The sedimentation rate is commonly elevated. Anemia may be absent in the early stages of the disease, but it is quite common in the later stages. Hematuria and albuminuria are frequent and occurred in 48 per cent and 65 per cent of cases respectively. It is again important to have repeated urine examinations to detect transient episodes of hematuria. Krupp<sup>26</sup> has described findings in the urinary sediment which he considered characteristic. These consist of large amounts of albumin, red cells, red cell casts, fatty casts, and waxy casts. A positive Wassermann reaction is at times seen, and in the past has given rise to the suspicion that syphilis may play a part in the etiology. Such positive serologic tests are frequently of the nature of a biologic false positive with low titers and a subsequent return to normal over a period of time. It has been observed that these patients tolerate transfusions poorly and it is suggested that atypical agglutinins may be responsible for this as well as for the serologic reactions. Serial electrocardiograms are of considerable importance and may at times be the only indication of coronary artery involvement. Tachycardia and flattening or inversion of the T-waves are the most common findings. Roentgen-ray examination is of little help, although in rare instances small areas of fibrosis or infarction can be detected in the lungs. Diagnosis in the final analysis rests upon study of a pathologic section. Biopsy of a subcutaneous nodule

or, in its absence, muscle biopsy may establish the diagnosis. The absence of a positive biopsy by no means rules out the diagnosis.

*Course.* Polyarteritis nodosa is usually of gradual onset, but the manifestations at times appear quite suddenly. The duration is more frequently many months, or at times years. The course may be punctuated by periods of remission and relapse. Recovery may take place in 5 to 10 per cent of the cases. This rate will undoubtedly increase with more frequent diagnosis. Only three of Grant's seven cases had died after three years.<sup>18</sup> Death is more commonly due to congestive heart failure.<sup>6a</sup> Uremia and hemorrhage are other not uncommon modes of termination.

The clinical features of this disease are illustrated by the following case reports.

#### CASE REPORTS

*Case 1.* I. B., colored male, aged 34, was admitted to Grady Hospital on August 21, 1939 and died January 4, 1940. Nine months before entry he developed a migratory polyarthrititis involving, at one time or another, the fingers, wrists, shoulders, elbows and ankles. The joints were acutely painful and swollen, and the attacks lasted from a few days to a week. Several weeks prior to the arthritis, he had had a painful swelling over his right testicle. During subsequent months he began to lose weight and complain of weakness. For about seven months he experienced a painful burning of the feet with occasional sharp shooting pain in the legs. There was gradual inability to use the feet and legs. Two months prior to admission he noticed a vesicular eruption over the trunk and extremities. This itched severely and was followed by scaling and pigmentation. There was progressive dyspnea on exertion for about two months and occasional paroxysmal nocturnal dyspnea. Since the onset there had been a nocturia of three to four times.

As a child he had had pertussis, chickenpox, measles and pneumonia. He had experienced two attacks of gonorrhea without complications, the last attack being in December 1938. Three ribs had been fractured two years previously.

Physical examination revealed a temperature of 100° F., pulse 112, respirations 24 and blood pressure of 156 mm. Hg systolic and 110 mm. diastolic. He appeared acutely ill and dyspneic, and complained of itching of the skin and a burning sensation in the legs. Over the trunk, back and upper arms there were numerous pigmented macular areas with some central scarring. There was a mild generalized lymphadenopathy. The retinal arteries showed an increase in the light reflex with an A-V ratio of 1 to 3, with many fine and diffuse hemorrhages around the discs and slight edema of the discs and the surrounding retina.

There were many crepitant and subcrepitant râles throughout both lung fields. The heart was slightly enlarged to the left and the apex impulse was felt in the fifth intercostal space about 10 cm. from the midsternal line. The first sound at the apex was split and was followed by a soft systolic murmur. The radial arteries were markedly sclerotic. The abdomen was distended and generally tender, but more so in the right lower quadrant. The liver was palpated 3 to 4 cm. beneath the right costal margin and was slightly tender. The patellar reflexes were hyperactive. The ankle jerks were absent bilaterally. There was diminished sensation to pin-prick. There was marked motor weakness of the muscles of both feet and legs with an inability to dorsiflex the feet. A slight foot drop was present on the right side. The extremities were wasted and the feet were edematous with tense skin. The patient complained of burning pain in the legs when stimulated.

The hemoglobin was 6.4 gm. with a red count of two million. There were 8,000

leukocytes with 83 per cent polymorphonuclears and 16 per cent lymphocytes. The urine specific gravity was 1.010 and contained 4 plus albumin, with 25-30 white blood cells per high power field and 10-20 red blood cells per high power field with 5-10 hyaline casts per low power field. The sedimentation rate was 150 mm. in one hour by the Westergren method. The value for the blood sugar was 62 mg. per cent, non-protein nitrogen 35 mg. per cent and creatinine 1.5 mg. per cent. The total protein was 6.3 gm. with 3.6 gm. albumin and 2.7 gm. globulin per 100 c.c. of blood. The spinal fluid was normal. The urine concentration test gave a maximum value of 1.012, the phenolsulfonphthalein excretion 35 per cent and urea clearance test 65 per cent. A bromsulphalein test was normal and an agglutination series was negative. Repeated blood cultures were negative. Repeated blood counts revealed marked secondary anemia with leukocyte counts which varied from normal to as high as 27,900 with a slight shift to the left and an eosinophilia of 4 per cent. Repeated urinalyses revealed albuminuria, many hyaline and granular casts and many pus cells. On January 4, 1940, the non-protein nitrogen was 60 mg. per cent and the creatinine 2.1 mg. per cent.

The patient had many and varied complaints. The temperature ranged from 99° to 103° F., and was of an irregular spiking type. The pulse ranged from 90 to 110. He complained of burning in the legs for about two weeks and following this developed thrombophlebitis of the right leg. Some strength was regained in the legs but the foot drop remained. There was frequent complaint of vague abdominal pain. Pulmonary edema occurred on one occasion, and on another there was an episode of vertigo, tinnitus, nausea, vomiting, profuse perspiration and weakness of the right side of the body for a period of 24 hours. A tender area appeared over the right third chondrosternal junction and remained for several days. After five and one-half months in the hospital he gradually became drowsy and then comatose with stertorous respirations and incontinence. He died quietly on the one hundred thirty-seventh hospital day.

*Case 6.* A second lieutenant, aged 31, was admitted to hospital December 31, 1942, complaining of pain and swelling of the hands and feet. The past history was non-contributory. He had received yellow fever vaccine in March, 1942, and was hospitalized in July, 1942 because of hepatitis, which was thought to be due to the vaccine. In October 1942 he noticed soreness of the calves of the legs. Subsequently there was diminished sensation over the dorsum of the left foot and along the anterolateral aspect of the leg. A few days later there occurred severe epigastric pain which lessened to a dull aching pain, lasting one week. He was admitted to the Station Hospital October 20, 1942. For a period of six to eight hours, he lost all sensation in the left foot. After two weeks he was returned to duty and all examinations were said to have been normal. There was recurrence of the soreness in the legs, and in addition, the ankles became red, hot and swollen. He was readmitted to the hospital and developed pain in both arms, particularly the left. The painful joints did not respond to salicylates. There was a low grade fever of 99° to 101° F. He developed numbness in the arms and legs and the brachial arteries became tender with some localized areas of swelling. There was a gradual loss of 35 pounds weight. There was anorexia, constipation, and on one occasion diarrhea. He developed a cough and nocturnal dyspnea. Upon admission to this hospital, December 31, 1943, the blood pressure was 190 mm. Hg systolic and 140 mm. diastolic. The peripheral vessels were markedly sclerotic. The retinal arterioles showed generalized constriction with increased light reflex, flame shaped hemorrhages, and a few areas of exudate. The heart was normal. The lungs contained scattered fine moist râles. There was hyperesthesia over the hands and lower legs and feet. There was a left foot drop with diminished knee jerk on the left and an absent knee jerk on the right. The left testicle was smaller than the right.

TABLE II

Case	Age	Symptoms	Signs	Laboratory	Duration	Pathology
1. M.	34	Migratory polyarthritis, painful swelling of rt. testicle, weakness, loss of wt., burning of feet, shooting pains in legs, inability to use legs. Vesicular eruption over body. Dyspnea, nocturia X 3-4, vague abd. pain. Pul. edema on 1 occas. Episode of vertigo, tinnitus, n. and v., with weakness of rt. side of body for 24 hr. 1 transient subacute nodule over thorax. Uremia. Hist. of urticaria, no hist. of sulfonamides.	Temp. 99 to 103, B.P. 156/110. Pigmented macular areas with central scarring, mod. ret. scl. with hemorrh. and exudates. Mild generalized adenopathy. Mild enl. of l. vent., sys. m. murmur, rales in lungs. Mod. rad. scl. Liver enl. 3-4 cm. beneath cm. Absent A.K. motor weakness of legs and ft. drop, wasting extremities.	R.B.C. 2 m., Hb. 6.4 gm., W.B.C. 8,000 to 27,900, sl. shift to left, max. eosinophilia of 4%, sed. rate 150. Urine alb. 4 plus, 25 to 30 W.B.C. and 10-20 R.B.C. per HPF, 5-10 hyaline casts per LPF. Fishberg conc. 1.012. PSP 35% 1 hr., urea cl. 65%. Sp. fl. normal. Total prot. 6.3 gm., alb. 3.6, glob. 2.7. Repeated agglut. series and bi. cultures neg. NPN 35-60.	14½ months	Periarteritis nodosa involving kidneys, heart, liver, mes. aa. Lesions were of all stages from acute to healed.
2. C. M.	32	Rx. for syphilis 5 m. Dev. cramping pain in abd. and diarrhea following infection of Bl. 6 wks. before entrance to hosp. Freq. gripping abd. pain and n. since, throbbing frontal headaches for several mo., loss of 20 lbs. No hist. of allergy or sulfonamides.	B.P. 180/120, occas. temp. of 100. Emaciated. Generalized abd. tenderness without rigidity, hyperactive peristalsis. Urticaria 1 occas. Dev. subarachnoid hemorrh. following laparotomy.	R.B.C. 5 m., Hb. 60%, W.B.C. 12,500-18,900 with eosinophilia 5-12%, sed. rate 109. Bl. sugar 68, NPN 27, creatinine. Urine-albumin 2 plus, few R.B.C. Sp. fl. neg. Kahn neg. Freq. occult bl. in stools. Ict. index and agglut. series normal. PSP 35% 1 hr. Retrograde pyelography, G.I. series and barium enema normal, EKG normal.	2½ months	Laparotomy revealed whitish nodules of the vessels of the mesentery and omentum, microscopically characteristic of periarteritis nodosa.
3. C. M.	29	Dull aching in epigas. and mid abd. 8 mo. aggravated by food, freq. n. and v., anorexia, loss of 18 lbs. Pain in both flanks, aching in legs. Noct. dysp. Tender nodules on abd. lasting 1 wk. Antisyph. Rx. 3 mo.	B.P. 205/140. Mod. ret. scl., sys. murmur mitral. Rhonchi in l. lung. Low grade fever of 100. Mild adenopathy generalized. Abd. tender, espec. over g.b. and loins. Several small nontender subcut. nodules on abd.	R.B.C. 3.9 m., Hb. 10 gm., W.B.C. 10 mo. 13,000-16,000 with 2-5% eosinophiles. Urine—alb. tr., few R.B.C., occas. gran. cast, Fishberg conc. 1.012. Bl. sugar, NPN normal. Sp. fl. Kahn 2 plus. G.A. normal. G.I. Series, G.B. series and barium enema normal. Retrograde pyelograms—double ureters and pelvis. Positive benzidine test on 1 stool.	10 months	Laparotomy revealed innumerable whitish nodules like BB shot of aa. of mesentery, stomach, pancreas, colon and g.b. Nodules extended as far as 1 inch along the aa. Infiltration of all coats with polys, lymphs and eosinophiles.
4. C. M.	15	Throbbing pains in feet after walking, 3 wks., intermittent claudication, numbness and "pins" in legs. Dull pain l. flank intermittently for 3 yrs. Paroxysmal cough 6 mo. with associated substernal pain, sev. attacks of asthma. Papular eruption on legs and abd. 9 mo. prior to entry. No history of sulfonamides.	B.P. 160/95, pulse 140, temp. 99-101. Thickened and tortuous, temp. aa., absent pulsations in legs, dim. temp. of ft. Excoriated papules of trunk and extrem. Rhonchi in lungs, systolic murmur at apex.	R.B.C. 5.7 m., Hb. 16 gm., W.B.C. 13,000-19,850 with 5-24% eosinophiles, sed. rate 47. NPN and sugar normal, urine neg., EKG normal.	Acute symptoms subsided after 3 mo. Pt. well 3 yrs. later except for occas. asthma.	Biopsy of temp. a. lumen filled with prolif. of fibroblasts and endothelial cells among which are scattered numerous eosinophiles and an occas. poly, some interstitial hemorrh. with a few polys in adventitia.

TABLE II—Continued

Case	Age	Symptoms	Signs	Laboratory	Duration	Pathology
5. W. M.	29	Operation for draining bronchial cyst; 2 weeks later dev. pain in upper and lower extremities, migrating polyarthritis, cramping abd. pain, edema of legs and face, neuritic pains in arms and numbness of left arm, palpitation, dyspnea and terminally severe precord. pain. Loss of 24 lbs. Subcut. nodules and purpuric eruption in region of ankles.	B.P. increased from 120/80 to 160/100, temp. 99-102, tachy. Subcut. nodules in region of ankles and purpura of ankles and forearms. Wrists and ankles red, hot, tender and swollen. Liver palpable 3-4 cm. beneath c.m. Edema of face and legs. Later dev. gallop rhythm and moist râles in lungs.	R.B.C. 2.6-4 m., Hb. 50-70%, W.B.C. 14,800-16,650 with 18 to 74% eosinophilia, sed. rate 18 (Cutler). Urine 1-1 plus, alb., many R.B.C. and W.B.C., freq. hyaline casts and gran. casts, sp. gr. 1.010. Urea chloride 86%. NPN, uric acid, chlorides, sugar, phosphorus, calcium, phosphatase and urea N normal. Platelets normal. PSP 10% in 1 hr. Icterus index 5. Kahn neg., agglut. series neg. Total prot. and A/G ratio normal. Sternal biopsy neg. Repeated bl. cultures neg. EKGs—progressive evidence of cor. insuff.	4 months	Marked edema of lungs, heart wt. 430 gm., whitish nodules along cor. aa., liver wt. 2360 gm., aa. of heart, kidney, adr. and mesentery show a chr. oblit. arteritis with scarring of media, extensive infl. with round cells, plasma cells and eosinophiles, lumen markedly oblit., pink fibrinoid present. Chr. inflammatory reaction in myocardium similar to aa.
6. W. M.	31	Yellow fever vaccine March 1942, hepatitis July 42. Oct. 42 calf m. soreness, hypesthesia left leg. Epigas. pain. Transient loss of sensation i. ft. Ankles red, hot and swollen. Low gr. fever. Numbness of arms and legs. Tender swellings along brach. aa. Loss of 35 lbs. Anorexia, constip., cough, nocturnal dyspnea, orthopnea, blurring of vision. Irrational. Severe pains in arms and legs. No hist. of allergy or sulfonamides.	B.P. 190/140. Emaciated. Temp. 99-101. Hyp. neuroretinitis. Heart slightly enlarged. Moist râles in lungs. Hypertrophia hands, legs and feet. i. ft. drop, abs. A.K. rt., dim A.K. l. Pitting edema of lower extremities, fibrill., muscle tremors, coma.	R.B.C. 3.5-4.3 m., Hb. 70-80%, W.B.C. 8,000-13,000, 7% eosinophiles 1 occas., sed. rate 45. Urea clearance 105%. PSP 35%. Fishberg conc. 1.011. Urine albumin 1-4 plus, freq. R.B.C. in cast. NPN 60. Ict. index 5. Urea N. 25, creatinine 2.7, uric acid 4.5. Serial EKGs with inversion of T-waves in all leads. Total prot. 6.1, A/G ratio 1.3-1. Bl. cultures and agglut. series neg. Calif muscle biopsy neg.	5 months	Heart wt. 370 gm., whitish nodules along cor. aa., nodular thickening of the mesentery aa., rt. kidney 130 gm., l. 140 gm., yellowish wedge shaped areas of infarction, infarcted aa. markedly thickened, aa. of liver show chr. oblit. process. Rt. lung 680 gm., l. lung 840 gm.
7. C. M.	42	Cramping epigastric pain 2 mo., throbbing pain in flanks, weakness, loss of wt., dysp. on exertion 3 wk., cough, fever, constip., nocturia X 2 for several yrs., loss of 58 lbs., irregular temp. as high as 102. Developed nontender nodules over legs and along temp. aa. Terminally dev. sudden severe pain in l. lower back radiating down l. leg causing paralysis of the leg. Known hypertension 5 yrs., unexplained fever for 1 wk. 3 mo. prior to P.I. No hist. of allergy or sulfonamides.	B.P. 198/120, temp. 102. St. rect. scl. Heart normal size, systolic apical murmur. Tenderness both flanks. Mod. periph. scl. Dev. transient nontender nodules pretibial region and along temp. aa. Terminally no pulsations could be felt in the l. femoral artery or aa. of legs. L. leg cold and could not be moved voluntarily.	R.B.C. 4 m., Hb. 10 gm., W.B.C. 15,000, normal diff., sed. 120. Kahn neg. Urine 1.021, tr. alb., occas. R.B.C., W.B.C. and hyaline cast. Repeated stools pos. for occult bl. Glucose tolerance 110, 180, 270, 280 and 220. NPN 29, total prot. 5.7, alb. 3.6, glob. 2.1. PSP 51%. Agglut. series neg. G.A. normal. G.I. series and barium enema normal. Pyelograms normal.	5 months	Periarthritis nodosa involving heart, kidneys, adrenals, pancreas, and liver. Dissecting aneurysm of aorta extending from aortic valve to bifurc. of aorta, intimal tear in region of l. subclavian artery. Heart wt. 340 gm. Rt. kidney 140 gm., l. kidney 110 gm.

TABLE II—Continued

Case	Age	Symptoms	Signs	Laboratory	Duration	Pathology
8. W. M.	21	Back pain radiating to scrotum. Headache, nausea and vomiting 1 mo.; blurring of vision. Dev. precord. pain, paroxysmal dysp., and signs of congestive failure. Hist. of treatment for syphilis in 1941. Painful swelling of ft., ankles, knees, and fingers for 1 mo., 6 mo. prior to entry.	B.P. 190/130, hyp. neurorretinitis, marked thickening and beading of radial and brachial aa. Stupor during last week of life. Temp. 99°-101°, pulse 90-110.	R.B.C. 4.8 m.-2 m., Hb. 99-45%. W.B.C. 15,000, normal diff. Urine sp. gravity 1.006, 2.4 plus alb., occas. cast, few W.B.C. and R.B.C., NPN 38 to 86, urea N 30. Kahn neg. Total prot. 4.8 with reversal of A/G ratio. Serial EKGs—progressive evidence of cor. insuff. with inversion of T-waves in all leads.	9 months	Healed periarteritis nodosa of kidneys, heart, pancreas, testicles and thyroid. Rt. lung 750 gm., l. lung 590 gm. Heart wt. 475 gm., irregular areas of scarring of myocardium, nodular thickening of cor. aa. Rt. kidney 100, l. 110, cortex measures 4 mm. Irreg. infl. of yellowish gray tissue through cortex and medulla.
9. W. M.*	41	Sore throat, easy fatigability, dysp. on exert., painless hematuria, occas. precord. pain, n. and v. burning sensation in abd., orthopnea, visual disturbances, itching of skin, nontender nodule over back, cough. Known hypertension for 8 yrs. Polyuria and nocturia succeeded by oliguria. No hist. of sulfonamides or allergy.	Temp. 99-101, pulse 120, B.P. 140/100-200/120. Marked ret. scl. with exudates. Heart enlarged. Slightly tender nodular pulsating mass 2 cm. in diameter at angle of rt. scapula. Mod. peripheral scl. Râles in lungs. Terminal coma.	R.B.C. 3.95 m., Hb. 56%, W.B.C. 18,000-29,000, 4% eosinophiles, slight shift to l. Urine sp. gr. 1.007, 3 plus alb. NPN 110-165, creat. 11.3-15. CO <sub>2</sub> combining power 24, urea N 100. Venous pressure 110, circ. 20 sec., EKG L.A.D., digitalis effect with inverted T in I and IV. Bl. sugar 128.	2½ months	Recent hemorrh. into wall of rt. cor. artery giving occlusion. Thrombosis of branches of hepatic artery, cystic a., rt. gastric a., both suprarenal aa., interlobar and interlobular aa. and testicular aa. Gran. contracted kidneys, uremic pericarditis, bronchopn., patent foramen ovale, pheochromocytoma rt. suprarenal.
10. W. F.	65	Dysp., pedal edema, intermittent epigastric pain, swelling of abd., orthopnea, night sweats, loss of wt., nocturia X 2-4, severe generalized abd. pain 3 days, nausea. No hist. of sulfonamides or allergy. Visited clinic 7-24-31, cardiac asthma, B.P. 134/70.	B.P. 140/95. Sl. cyanosis. Temp. 98.4, pulse 110-120. Heart sl. enl., liver enl. 6 cm. beneath c.m., mild ascites. Petechiae over both legs. Enl. l. supraclavicular node. Terminal coma.	R.B.C. 3.7 m., Hb. 12.8 gm., W.B.C. 12,900-15,850, 10% eosinophiles, urine sp. gr. 1.023, alb. 2 plus. Total prot. 6.6, alb. 5.1, globulin 1.5. Kahn neg. NPN 47, aug. 102. Tach. A-ra reaction positive. EKG L.A.D. abs. R <sub>4</sub> , low T <sub>1</sub> T <sub>2</sub> . G.b. series normal, G.I. series neg. X-ray of heart—marked cardiac enl., diffuse pul. congestion.	1 year	Laparotomy showed enl. liver with granular appearance. Ecchymoses of small intestines. Sections of liver reveal periarteritis nodosa.
11. C. M.†	39	Known hypertension 6 mos., n. and v. anorexia, night sweats, itching of skin and light colored stools 1 wk., fever, 2 episodes of severe epigastric pain followed by persistent abd. discomfort. No hist. of allergy or sulfonamides.	B.P. 210/160, pulse 80, temp. 99-101.8. Sl. generalized lymphadenopathy. Icteric sclerae. Ret. scl. with hemorrh. and exudate, palpable liver, tenderness RUQ. Flat film of abd., diffuse density in rt. upper abd., pyelograms showed ant. displacement of rt. kidney with surrounding soft tissue mass, slight elev. of rt. diaphragm.	W.B.C. 10-26,000, icterus index 125, urine 4 plus alb., occas. R.B.C. and W.B.C. Sed. rate 27. PSP test 60%. Kahn neg.	Still alive	Mass in region of rt. kidney removed, wt. 685 gm. Kidney and adrenal completely encased in hemorrhagic fat tissue 1-4 cm. wide. Hemorrhage outside capsule and also subcapsular. Two aa. are ad. to hemorrh. Micro.—ruptured interlobar a., fibrinoid degen. of media, subacute inflamm. cell infiltration with eosinophilia. Fibrinosis of media.

\* Reported previously by Wolff.<sup>47</sup>

† Reported through courtesy of Dr. Chester Fort and Dr. Walter Sheldon.

Patient continued to complain bitterly of pain in the arms and legs and opiates were necessary for relief. Nocturnal dyspnea was severe but responded somewhat to digitalis and salyrgan with a marked clearing of the pulmonary congestion as evidenced by roentgenogram. This improvement was only temporary and marked edema of the lower extremities appeared. There was pain in the right upper quadrant which was attributed to congestion of the liver. He complained of blurring of vision coincident to hypertensive neuroretinitis. During the last two weeks of life he was irrational, exhibited fibrillary muscle tremors, and presented the picture of uremia, dying in coma March 20, 1943, five months after onset of symptoms.

Serial electrocardiograms (figure 1) showed persistent tachycardia with evidence of progressive coronary insufficiency as shown by inversion of the T-waves in Leads II, III and IV and flattening of the T-waves in Lead I. There was a moderate anemia, the red cell count varying between 3.5 and 4.3 million with a hemoglobin of 70 to 80 per cent. The leukocyte count varied from 8,000 to 13,000. On one occasion 7 per cent eosinophiles were present, but on other occasions the differential count was normal. The sedimentation rate was 45 mm. in one hour. Repeated urinalyses showed 1-4 plus albumin with frequent red cells and hyaline casts. The phenolsulfonphthalein test showed 35 per cent excretion of the dye in one hour. On March 9, 1943, the non-protein nitrogen was 60, urea nitrogen was 25, uric acid 4.5, and creatinine 2.7 mg. per 100 c.c. The total protein 6.1 gm. per 100 c.c. with an A/G ratio of 1.3 to 1. Repeated blood cultures and agglutination tests were normal. A calf muscle biopsy was negative.

The findings in 11 cases are presented in tabular form in table 2.

#### COMMENT

Of 11 cases of polyarteritis nodosa, 10 were male and one was female. The ages ranged from 15 to 65. The duration of the illness varied from two and one-half months to one year, with recovery in one patient who was alive and well two years later. Hypertension was present in every patient at some time during the course of the disease. Leukocytosis was noted in every case and eosinophilia was present in five patients. A diagnosis was made in each instance during life, on three occasions by laparotomy. Case 11 developed a perirenal hemorrhage and nephrectomy was performed because of a suspected neoplasm. Case 7 died of a dissecting aneurysm which was unrelated to polyarteritis, there being no evidence of such disease in the aorta. Four cases showed clinical and pathologic evidence of involvement of the coronary arteries with progressive electrocardiographic evidence of coronary insufficiency (figures 1, 2, 3). Three patients showed clinical or pathologic evidence of involvement of the testicular arteries.

#### SUMMARY

Eleven cases of polyarteritis nodosa are reported. The recent English literature is reviewed and the symptoms of 177 cases are tabulated. Serial electrocardiograms demonstrating progressive involvement of the coronary arteries in three cases are recorded. A case of apparent spontaneous cure of two years' duration is reported.

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# SOME UNUSUAL THORACIC COMPLICATIONS OF TYPHOID AND SALMONELLA INFECTIONS \*

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THE authors have had the opportunity of observing a case of typhoid empyema with bronchopleural fistula, and a case of *Salmonella* costal chondritis. They have also had access to the records of one case each, of the following conditions: typhoid costal osteochondritis; pure typhoid empyema; typhoid lung abscess; and *Salmonella* empyema. We believe that these complications are sufficiently rare to justify reporting in some detail.

## PULMONARY COMPLICATIONS OF TYPHOID FEVER

Fifty years ago the French clinicians were singularly aware of some of the pulmonary and pleural complications of typhoid fever. In 1884, Sahli<sup>1</sup> reported the isolation of the typhoid bacillus from the sputum, and Jehle<sup>2</sup> found it present in nine of 15 cases in which he examined the sputum. Bronchitis is an almost constant part of typhoid fever, often being mild and evidenced only by a more or less productive cough. Occasionally, however, the bronchitis is severe, with profuse sputum, blood streaking or even frank hemoptysis, generalized sibilant râles, dyspnea, and cyanosis.<sup>3,4</sup> Such a process was difficult to distinguish from a pneumonitis or, as it was then called, congestion, which generally affected the bases posteriorly. Caussade<sup>5</sup> even reported a generalized pulmonary edema, from the fluid of which *B. typhosus* was obtained in pure culture. Roque and Bancel<sup>6</sup> obtained the bacillus six times in 16 aspirations of the lung. Bronchopneumonia was a slightly more advanced stage of the same process, characterized, in addition, by signs of patchy consolidation. There are many postmortem reports of "congestion" and bronchopneumonic foci from which the organisms were cultured.<sup>2,6</sup> These foci were noted by several observers to be more hemorrhagic than those of ordinary bronchopneumonia. It would be impossible to estimate the proportion of specific to ordinary pyogenic bronchopneumonias, but certainly the latter occurred.

Lobar pneumonia was quite rare and, when it occurred, was usually suspected of being pneumococcic. This was probably true when the complication appeared after the disease was well established. The pneumococcus was often found in the sputum and rarely both this organism and the typhoid bacillus were present. Busquet<sup>7</sup> reported three cases which developed clinical pneumonia and had blood cultures positive for both *B. typhosus* and

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pneumococci simultaneously. Nevertheless, pure lobar typhoid pneumonia did occur. As such, the pulmonary symptoms and signs tended to dominate the picture, the abdominal findings being minimal or absent. This syndrome, which was referred to as "Pneumotyphoid," was similar to pneumococcic lobar pneumonia except for its relatively long duration and the variable presence of symptoms referable to the abdomen. Vitug and Cruz<sup>8</sup> have reported a case of right lower lobe consolidation in which the sputum and blood cultures were positive for *B. typhosus*, the fever having lasted for 29 days. A palpable spleen was the single abdominal abnormality, although the stools and urine were not cultured.

The occurrence of pulmonary infarction is to be expected, as a result of the frequency of thrombophlebitis in typhoid fever. Many of the early authors assumed that the presence of bloody sputum, with or without a friction rub and signs of localized consolidation, was evidence of infarction. This assumption quite possibly gave a false impression of the incidence of infarction; but rare postmortem reports testify that it was a real possibility. Robinson<sup>9</sup> reported a case in which, at autopsy, the artery of the right lower lobe was plugged by a thrombus. A very large abscess occupied almost the entire lobe. In addition, there was a small basal empyema and the left lung contained scattered patches of bronchopneumonia. The abscess, pleural fluid, thrombus and left lung were all positive for *B. typhosus* in pure culture. Flexner and Harris<sup>10</sup> had previously reported a similar case. Finley<sup>11</sup> and McNaughton and Rhea<sup>12</sup> reported the postmortem discovery of a fresh infarct of the left lower lobe, with a hemorrhagic pleural effusion positive in pure culture for *B. typhosus*.

Abscess is perhaps the rarest pulmonary complication of typhoid. Basch,<sup>13</sup> Chini,<sup>14</sup> and Harvill,<sup>15</sup> among others, have reported abscesses in which the organisms were cultured from the sputum. The symptomatology apparently does not differ from that of other types of abscess, although it is probably milder than in the putrid type; the prognosis, with respect to the abscess, is certainly better. The excavation of large infarcts occasionally produces a cavity, but most abscesses are probably formed by necrosis of a locally intense specific pneumonic process. Multiple abscesses have been encountered in the moribund having an overwhelming typhoid infection.

As an example of this form of pathologic lesion we would like to cite Harvill's unusual case, which was reported from the University of Michigan Hospital in 1942. On the admission of a young typhoid fever patient, the roentgenogram of the chest was negative. Several weeks later, following a small hemoptysis, a second film of the chest revealed the presence of a small abscess cavity in the periphery of the left upper lung. The sputum was positive for *B. typhosus* on culture, and concentrate examination and culture were negative for tubercle bacilli. Subsequent films showed gradual resolution of the light infiltration surrounding the cavity and the patient made a satisfactory recovery, although at the time of discharge a small pneumatocele persisted at the site of the abscess. A recent follow-up reveals that he is

working and apparently asymptomatic. The pulmonary defect was present, essentially unchanged, as late as April, 1943.

### PLEURAL COMPLICATIONS OF TYPHOID FEVER

Before the discovery of *Bacillus typhosus* by Eberth in 1885 the French authors were remarking upon the rarity of pleurisy, while the English and German, on the contrary, were insisting on its frequency. Subsequently, typhoid pleurisy was thoroughly studied, particularly in France. Its incidence, like that of other complications varies with the epidemic as well as with the attention of the clinicians and the frequency of thoracentesis. Cantegril<sup>10</sup> concludes that effusion occurs in about 2 per cent of cases of typhoid fever, although less than 0.5 per cent and as high as 7.6 per cent have been reported. A form of pleurotyphoid has been described which, analogous to pneumotyphoid, is characterized by predominance of pleuritic symptoms with the early formation of rather large amounts of fluid. In such large early effusions the toxicity may be overwhelming.\* Ordinarily the effusions are small and develop after the disease is well established or during its decline. A subjacent specific pneumonitis is almost always present, as shown by the presence of cough, sputum and basal râles; the râles often persist throughout the course of the pleurisy if it is not too massive to dampen them. The symptoms do not differ materially from those of ordinary pleurisy. Pain is usually present early and a friction rub can be heard at this time. The temperature, pulse, and respirations show slight increase and, after two or three days, fluid is present in moderate amounts.<sup>11</sup> Characteristically, the effusions are smaller than the physical signs would indicate.<sup>10</sup> There may be signs and symptoms of pleurisy, but no effusion. Mouriquand<sup>3</sup> observed a group of pseudopleurisies which had all the signs of effusion but yielded no fluid. He felt that these represented symptomless low-grade consolidation.

The pleural fluid is serofibrinous, hemorrhagic or, rarely, purulent. It contains leukocytes in varying numbers and types. Widal has stressed the presence of large endothelial cells, supposedly from the pleura. The agglutinating power against the bacilli becomes increasingly strong but is usually weaker than that of the blood. The fluid is also increasingly bactericidal<sup>17</sup>; this fact probably accounts for the occasional failure to culture *B. typhosus* from it, or the disappearance of the organism from later specimens. The course of this effusion is benign and its presence apparently has little or no effect upon the mortality rate. It resorbs in from a few days to a few weeks, a single aspiration often being sufficient. It was Nordmann's<sup>18</sup> opinion that pleurisies which occur during convalescence are very apt to be tuberculous. Other authors disagree with this opinion. The concurrence of typhoid and tuberculosis is an obvious possibility. The former could well precipitate a tuberculous effusion; cases have been reported in which both

\* See Case 1.

organisms were obtained from the fluid by culture and animal inoculation, respectively.<sup>17</sup>

Pyogenic infections of the pleura may occur alone or with typhoid pleurisy. Empyemata containing *B. typhosus* and pneumococci, streptococci, staphylococci or *B. coli* have been observed. Macaigne<sup>19</sup> reported a loculated empyema; one pocket yielded thick pus which was positive for *B. typhosus*; another contained thin serosanguineous fluid from which a pure culture of *B. coli* was obtained. A few observers have found these two organisms simultaneously in the blood stream\*; this association suggests a possible etiologic relationship to ulceration in the intestinal tract.

The persistence of a typhoid effusion as a pure or mixed-infection typhoid empyema, or the development of a pyogenic empyema during the course of typhoid fever causes a mortality rate which Jandl<sup>20</sup> estimates to be from 15 to 20 per cent. Fortunately the incidence of empyema is extremely rare. Correia Neto and Finocchiaro<sup>21</sup> calculate that the number of typhoid empyemata varies from 1 to 2 per cent of the reported cases of exudative pleurisy (0.04 per cent of all cases of typhoid fever). Empyemata have been treated successfully by aspiration alone, or by intercostal drainage. As in other types of pyogenic empyema, however, the mortality, as well as the morbidity rates, are probably lower when rib resection for adequate drainage has been used.

Most empyemata apparently arise as effusions, which, for some reason, perhaps the character of the underlying pulmonary disease, persist and become purulent. Massingham<sup>22</sup> regarded his case as being due to infarction of the lung. An occasional right-sided empyema has been observed following hepatic or subdiaphragmatic suppuration, and Montel<sup>23</sup> observed one on the left side following a splenic abscess. A possible etiologic mechanism may be transpleural spread from a parasternal node, diseased cartilage, or infected rib. In Lane's case<sup>24</sup> a 54 year old man, who had had typhoid fever 40 years previously, developed a large empyema, the pus from which was positive for *B. typhosus*. It was thought that it might have resulted from typhoid osteitis of a rib.

#### CASE REPORTS

*Case 1.* J. T., a 26 year old white man, was admitted to the University of Virginia Hospital on November 17, 1929, with complaints of chills and fever, headache and joint pains. The patient had been well until four days before admission, when he began to feel drowsy and feverish. Profuse sweats, chills, severe headache, extreme weakness, and generalized joint pains developed within the next two days. There had been no nausea, vomiting, diarrhea, abdominal pain, or epistaxis.

Physical examination on admission to the hospital revealed a well developed, well nourished young man who appeared acutely ill. The temperature was 104° F., the pulse rate 100, and the respiratory rate 24. Rose spots were present over the abdomen. There was slight tenderness in both lower quadrants of the abdomen, with slight involuntary spasm. The liver and spleen were both slightly enlarged. Examination of the chest was negative.

\* See Case 2.

Laboratory studies revealed a normal urine; hemoglobin 90 per cent, with a red cell count of 4.3 million; and a white cell count of 4,900, the differential count being normal. Examination of the stool was negative. Although cultures of blood, urine, and stool were repeatedly negative for *B. typhosus*, the serum Widal agglutination was positive. A diagnosis of typhoid fever seemed justified on the basis of the clinical picture and the laboratory studies.

The patient ran the usual toxic course of typhoid fever without complications for 10 days. His temperature ranged constantly between 103 and 104° F., and his pulse rate averaged 90 to 100. On the tenth hospital day he developed a pleural effusion on the left side. Since there were neither distressing symptoms nor a change in the course of his illness, thoracentesis was deferred until five days later when his general appearance became worse and the pulse increased. At this time, December 5, 890 c.c. of thin, brownish-red, purulent fluid were removed from the left pleural space. This fluid had a specific gravity of 1.020, and microscopically showed innumerable polymorphonuclear leukocytes in each high power field. Bacteriologic studies yielded a pure culture of *B. typhosus*. During the next two days the patient became much worse, with marked prostration and a temperature of 106° F. On December 7, 500 c.c. of fluid, somewhat thicker and more purulent than that previously aspirated, were withdrawn from the left pleural space. Culture of this fluid was also positive for typhoid organisms. The surgical consultant did not advise immediate thoracostomy because the fluid, in his opinion, was still too thin. The patient's temperature rose to 106.8° F. and his pulse to 180, and, in spite of stimulants, he died on the following day. An autopsy was not performed.

*Case 2.* A. R. M., a 20 year old white man, was admitted to the University of Virginia Hospital on October 24, 1943, complaining of fluid in his right chest and of shortness of breath. He was well until six weeks previously, when he had had a gradual onset of malaise, anorexia, headache and fever. A week later he began to have dull pain in his lower abdomen. At times he was stuporous and delirious, and weakness progressed to prostration. A physician was finally called 10 days after onset. His clinical picture and a potentially polluted supply of drinking water suggested the diagnosis of typhoid fever. Four days later dyspnea and a sense of fullness in the right side of the chest developed, and examination revealed dullness in this region. On admission at this time to a community hospital, the patient's temperature was 103° F., the respirations 30, and the pulse 118. He appeared dull and apathetic; rose spots were present over the chest and abdomen, and there were signs of pleural fluid on the right side posteriorly. Examination of the abdomen was negative.

Laboratory studies revealed a white blood count of 13,000, with 91 per cent polymorphonuclear cells and a hemoglobin of 88 per cent (Sahli); urinalysis was negative except for a two plus test for albumin; the blood culture was negative; Widal agglutination was positive on two occasions; cultures of the stool were at first negative but later positive for *B. typhosus*. A roentgenogram of the chest was essentially negative, but a second one a week later showed a moderate accumulation of pleural fluid in the right base. Thoracentesis was performed on October 9, and again on October 10, and small amounts of yellowish-red, thin, foul pus were aspirated. Cultures of this pus were positive for *B. typhosus*.

The temperature pursued a septic course of from 100 to 105° F., in spite of five days of sulfadiazine treatment. After the second thoracentesis the patient developed a productive cough, which was worse when he lay on his good side; and the sputum was foul and grossly similar to the pus aspirated from the right pleural space. The downhill, septic course persisted until the patient's admission to the University of Virginia Hospital on October 24.

Physical examination revealed an acutely ill, poorly nourished white boy, with a temperature of 103° F., pulse 124, and respirations 28. Significant physical findings were limited to the right side of the chest, where there were flatness to percussion and absent breath sounds and tactile fremitus from the sixth rib posteriorly to the diaphragm. The hemoglobin was found to be 78 per cent; the red cell count was 3.8 million; and the white cell count 15,200 with 71 per cent polymorphonuclear cells. Urinalysis was negative except for 3 to 4 white blood cells per high power field. The blood Wassermann reaction was negative. A two plus benzidine test was the only abnormal finding in the stool. The blood culture was positive for *B. coli* and *B. typhosus*, but the Widal was negative. Culture of the urine was negative, but culture of the stool was positive for typhoid organisms, with a four plus agglutinating titer in a dilution of 1:6400.

Roentgenograms disclosed a massive hydropneumothorax on the right, with the right lung at least two thirds collapsed. The left lung was clear; thoracentesis soon after admission yielded 450 c.c. of rather thick, very foul, greenish-yellow pus. Smear of this pus revealed the presence of many Gram-negative bacilli and culture was positive for *B. typhosus*.

Forty-eight hours after admission to the hospital thoracostomy under local anesthesia was performed. A four centimeter segment of the eighth rib was resected in the midaxillary line and a greatly thickened pleura incised. Approximately 800 c.c. of thick, foul pus were aspirated, and a closed system of drainage was instituted. On the second postoperative day the temperature became normal and remained so until the eleventh day, when it again rose to 101° F. For the succeeding 16 days the patient was febrile, with temperature as high as 104° F. Since roentgenograms of the chest revealed rapid expansion of the lung with adequate drainage of the residual small empyema pocket, the fever was attributed to a recrudescence of the systemic infection. This impression was confirmed by the fact that the blood cultures, which had become negative after thoracostomy, again revealed the presence of *B. typhosus*. The temperature became normal again on the twenty-eighth postoperative day and remained so until a second recrudescence 10 days later. This episode lasted nine days, with a maximum temperature of 102° F. The convalescence was then uneventful until the patient's discharge 78 days after admission. There had been a rapid return of his strength and weight, and he was ambulant.

Repeated cultures of the blood, urine, feces, and wound drainage were negative for typhoid organisms before discharge; roentgenograms of the chest revealed slight pleural thickening in the costophrenic sulcus but no pleural pocket was demonstrable. The bronchopleural fistula, suspected from the history, and demonstrated by iodized oil injection of the pleural pocket during convalescence, had closed. A small catheter which was left in the sinus on discharge from the hospital was gradually shortened, and finally removed completely on February 25, 1944. The superficial defect epithelialized in a few days. At the final examination on March 18, 1944, the patient was found to be in excellent condition with no recurrence of symptoms.

### TYPHOID OSTEOCHONDRITIS OF THE RIBS

Typhoid involvement of the skeletal system is confined to the long bones, to the ribs and costal cartilages, and occasionally to the spine.<sup>25</sup> These lesions are not common, since as late as 1926 the Mayo Clinic had observed only three cases of typhoid osteitis.<sup>26</sup> They usually first appear during convalescence. The chief symptom of costal chondritis is anterior chest pain, often of a pleuritic character, which is followed by a tender, indolent swelling usually over the region of the sixth to ninth cartilages: a "cool" abscess.

This may regress and even disappear, but more often it ultimately ruptures to form a chronic sinus which drains for years and is a dangerous source of typhoid organisms. There are few if any systemic symptoms, and the lesions are amenable to surgery.

*Case 3.* J. F., a 32 year old man, was admitted to the University of Michigan Hospital, August 13, 1934, with the complaint of persistence of a draining sinus of his chest wall. In June, 1933, he had had typhoid fever. During the five weeks of his illness a tender area developed on the right upper thoracic wall anteriorly. A few weeks later a fluctuant swelling arose on the right lower thoracic wall; this was incised and became a chronic sinus. In December, 1933, the upper area finally became a sinus. Both sinuses were variously treated with irrigation, curettage, and subcutaneous typhoid vaccine. Seven weeks after onset of the original illness a small, tender, painful swelling became evident on the anterior left shin, eventually disappearing a year later. The chest sinuses discharged small sequestra and continued to drain. The pus from each was positive on culture for *B. typhosus*, and the patient was placed on the typhoid carrier list of the Michigan Department of Health.

Physical examination revealed a well developed, well nourished white man. The temperature was 100° F., the pulse 90, and the blood pressure 120 mm. Hg systolic and 70 mm. diastolic. A small draining sinus was present in the center of an irregular scar over the right third costochondral region, 6 cm. to the right of the mid-sternal line. A larger sinus surrounded by tags of granulation tissue was found over the right costal margin 9 cm. lateral to the midline. Both drained creamy pus. The liver was palpable 1 cm. below the right costal margin, but no other abnormalities were found. Roentgenograms of the chest and studies of the right clavicle, scapula, and upper humerus revealed no pathological changes. A roentgenogram of the left tibia revealed a very faint localized area of cortical thickening on the crest at the junction of the upper two thirds. The blood Kahn reaction was negative. Cultures taken from the sinuses yielded *B. typhosus*, *Staphylococcus aureus*, and a non-hemolytic streptococcus. Cultures of the stool and urine were negative for organisms of the typhoid-dysentery group. Agglutinations were positive for *B. typhosus* in a dilution of 1:320, but were negative for *B. melitensis* and *B. abortus*. Biopsies from the two sinuses revealed vascular pyogenic granulation tissue without distinctive features.

On August 18, 1934, an operation was performed by Dr. John Alexander. Under nitrous oxide-oxygen anesthesia the sinus of the upper lesion was excised to the second cartilage, which appeared somewhat expanded. Since the sinus continued into the cartilage, this was removed subperichondrally into the rib and sternum. The excised cartilage contained an abscess which was full of purulent granulations. The lower lesion was similarly treated. It involved the seventh cartilage, which was resected, together with the sixth. Two small tears were made in the pleura, but the lung was kept expanded under positive pressure until these were closed. The deep tissues were built up with sutures and the skin closed without drainage. The post-operative course was completely uneventful. The temperature never exceeded 100.2° F. during the first week, and was normal thereafter. The wounds healed *per primum* and the patient was discharged September 7. He was seen as an out-patient August 25, 1936. He had had no further symptoms and the wounds had remained healed. One year after operation he was released from the carrier files of the Department of Health.

Examination by the Department of Pathology of the tissue removed at operation showed the presence of a chronic, purulent osteomyelitis, with nothing pathognomonic of typhoid infection.



## SALMONELLA INFECTIONS

Of the many types of *Salmonella* organisms the five common ones are *S. paratyphi A* and *B*, *S. typhi murium*, *S. enteritidis*, and *S. cholerae suis* (*S. suipestifer*). Infection with these organisms assumes a much more protean form than the "paratyphoid fever" of earlier writers. Three clinical types are now recognized: (1) *Salmonella* gastroenteritis, which is characterized by a short incubation followed by an explosive, febrile gastroenteritis. Whereas all serologic groups may produce it, *S. typhi murium* is the commonest agent. (2) *Salmonella* fever,<sup>27</sup> which is somewhat analogous to the clinical picture of typhoid fever. It is usually caused by *S. paratyphi A* and *B*. Infection with the *A* organism is marked by fever and bacteremia, but usually no enteritis, while infection with *S. paratyphi B* produces fever, enteritis, and occasionally visceral abscesses. A large spleen and rose spots may be present, but not as regularly as in typhoid fever. (3) *Salmonella* septicopyemia. The members of the C serologic group, particularly *S. cholerae suis*, are most often responsible for this type of infection. There is marked invasiveness (60-66 per cent of the cases have a positive blood culture) with a tendency to bone and visceral localizations. Pulmonary involvement is especially common.

*Pulmonary and Pleural Infections.* In general, the pulmonary complications of *Salmonella* infections are similar to those of typhoid fever, except that they are probably more numerous.<sup>28</sup> Most of the cases reported prior to 1930 were due to *S. paratyphi A* or *B*. The pneumonic and bronchopneumonic lesions do not have the hemorrhagic character often seen in typhoid.<sup>29</sup> Jameson and Signy<sup>30</sup> reported a fatal case of *S. paratyphi B* infection in a child. Postmortem examination revealed consolidation of the right upper lobe and the apex of the lower. *S. paratyphi B* and *B. coli* were cultured from the consolidated area and from a succulent hilar lymph node. Thimm<sup>31</sup> reported a case in which a paratyphoid empyema developed. A pulmonary abscess was present in the partially collapsed lung, and both the pleural pus and the sputum were positive for *S. paratyphi B*. Abram and Glynn<sup>32</sup> observed a patient in whom pleurisy occurred three months after "influenza." The pleural fluid was at first clear but later became purulent, and eventually required resection of a rib. *S. paratyphi B* organisms and a streptococcus were cultured from the fluid initially, and later from the pus. Bullowa<sup>33</sup> was one of the first to report pulmonary infection with a *Salmonella* organism other than *S. paratyphi A* or *B*. In a fatal case of right middle lobe pneumonia *S. suipestifer* (*S. cholerae suis*) was grown from the sputum and from fluid aspirated by postmortem puncture of the lung. There have been several reports of bronchopneumonia associated with the septicopyemic type of infection.<sup>34, 35, 36</sup>

*Case 4.* Mrs. F. M., a 23 year old housewife, was admitted to the University of Michigan Hospital June 3, 1943, with the complaint of "swelling of the abdomen."

She had been well and active until two years previously, when she first noticed weakness, dyspnea, and loss of weight. Following her marriage abdominal enlargement became gradually apparent. This was followed by nausea and vomiting, amenorrhea, and edema of the feet and ankles. She entered a hospital in December, 1941, where several diagnoses were entertained, but none was confirmed. Attempts at abortion were unsuccessful, and paracentesis and diuretics were employed with moderate success. In April, 1942, a diagnosis of Banti's syndrome was made and splenectomy was performed. Following this she was much improved until a respiratory infection in November, 1942, initiated pleurisy, a productive cough, and a recurrence of dyspnea. The patient stated that clear fluid was removed from both pleural cavities on several occasions. Swelling of the abdomen and of the feet and ankles recurred and persisted. There were no familial diseases and the past history was unimportant.

Physical examination revealed a fairly well developed young woman who was pale, emaciated, and dyspneic, and who coughed frequently. The temperature was 99.6° F., the pulse 124, and the respiratory rate 32. Examination of the chest elicited signs of massive effusion on the left, and minimal dullness at the right base posterolaterally. The heart was at the upper limit of normal size with a heaving impulse transmitted to the precordium. The rhythm was regular and the sounds were loud, with a third sound audible at the apex. The liver was palpable three fingers'-breadth below the right costal margin and massive ascites was present, as well as a four-plus pitting edema of the feet and legs. The blood pressure varied between 124 and 84 mm. Hg systolic and 74 and 66 mm. diastolic. The venous pressure was 245 mm. of saline. Roentgenograms of the chest showed the presence of a large pleural effusion on the left, with a small amount of fluid in the right costophrenic sinus. The hemoglobin was 97 per cent (Sahli), the red cell count 5.3 million, and the leukocyte count 12,600 with a normal differential. The blood Kahn reaction was negative. The voided urine was negative except for a one-plus albumin. A benzidine test on the stool was very weakly positive, but there was no gross blood, mucus, ova, or parasites. The serum protein determination was 6.1 grams per cent. A single direct smear of the sputum was negative for acid fast bacilli. A bromsulphalein test showed no retention of the dye at the end of 30 minutes.

Aspiration of the left pleural space yielded 750 c.c. of thin pus from which was grown a gram negative bacillus with the cultural characteristics of the Salmonella group. It was agglutinated by *S. paratyphi B* and *S. typhi murium* sera. No acid fast organisms were found on smear or culture of either sputum or pleural exudate, and the tuberculin was negative (1:10,000 Mantoux). Stool cultures were negative for organisms of the typhoid-dysentery group. The pus was largely evacuated from the empyema space by thoracentesis and the cultural findings confirmed.

A diagnosis of constrictive pericarditis had been made, but it was felt that no operative treatment for this condition could be undertaken until the empyema had been successfully treated. Accordingly, on June 24, 1943, the empyema was drained by resection of a segment of the tenth rib posterolaterally, with the insertion of a water-sealed drainage tube. The parietal pleura was quite thick; a biopsy showed it to be lined with vascular pyogenic granulation tissue. No tubercles were found but lipophages were present in the granulation tissue. In July and August heavy diuresis was produced with ammonium chloride, Mercupurin, and Salyrgan. The ascites decreased markedly but soon began to reaccumulate. Throughout September and October a salt-free diet and Mercupurin were given, and continuous gentle suction was applied to the empyema drainage tube to encourage obliteration of the space. Roentgenographic measurements revealed a normal heart size, but fluoroscopy showed a limited amplitude of pulsation, especially along the right cardiac border. On August 31, 1943, a culture from the empyema showed the presence of *B. coli*, *B.*

*alkaligenes*, a non-hemolytic streptococcus, and *Staphylococcus aureus*, the latter predominating. On September 6, 1943, the same organisms, with the exception of *B. coli*, were found, and, in addition, a bacillus of the Salmonella group which failed to agglutinate with specific sera. On November 11, 1943, *S. cholerae suis* (Kunzendorf var.) was identified by cultural and serological methods, and *Staphylococcus aureus* and diphtheroid organisms were present. The empyema cavity progressively decreased in size and the sinus was healed by December.

On November 17, 1943, the patient left the hospital against advice but was re-admitted December 8, 1943. On December 16, 1943, 240 c.c. of pink fluid were aspirated from the right pleural space, culture of which revealed two species of non-pathogenic gram positive bacilli. Culture for acid fast bacilli was negative. On February 12, 1944, pericardiectomy was done by Dr. Cameron Haight. The heart was found to be encased in a heavy pericardial scar 1-2 mm. in thickness over the left ventricle and 3-4 mm. thick over the right. During operation the blood pressure was initially 104 mm. Hg systolic and 88 mm. diastolic. On release of the right ventricle the pulse improved and the blood pressure immediately rose to 126 mm. Hg systolic and 100 mm. diastolic; by the end of the operation one and one-half hours later the diastolic pressure had fallen to 86 mm. Hg. The pathological report of a portion of the removed pericardium was simply: "Dense hyaline scar containing lime salts—no tubercles." Convalescence was uneventful except for the development of a paranoid state. On February 20, 1944, the blood pressure was 98 mm. Hg systolic and 80 mm. diastolic, and the venous pressure was 245 mm. of saline. Her paranoid and schizoid symptoms became worse and when she was finally discharged March 15, 1944, plans were being made to commit her to a state institution.

*Chondritis.* Lindberg<sup>37</sup> described costal chondritis as a common sequel during the Russian typhoid-paratyphoid epidemic of 1919-1923. It was usually associated with a "paratyphoid" relapse. He clearly outlined the pathogenesis of intrachondral and perichondral abscess, with final contiguous spread to adjacent cartilages. Brock<sup>38</sup> reported a *S. paratyphi B* costal chondritis with intrachondral abscess, which occurred 14 years after an attack of gastroenteritis. The patient was cured by radical excision of the diseased cartilage.

*Case 5.* M. L., a 53 year old white man, was first seen at the University of Virginia Hospital, March 18, 1943, complaining of a swollen area on his right anterior chest wall. Three months previously he had first noticed a slight, non-tender swelling in the region of the fifth cartilage just to the right of the sternum. This tumor had been preceded by a severe cough from a respiratory infection which subsided after the usual course. There was no history of trauma. Gradually the swelling increased and became painful, while the skin over the area became hyperemic. There had been no spontaneous drainage, no chills, fever or sweats, and no other systemic symptoms except a loss of eight pounds in weight during the past year. The past history was negative except for influenza in 1918 and occasional mild pleuritic attacks. One brother had died of tuberculosis, but to his knowledge the patient had never had this disease. There was no history of obscure fever or severe attacks of enterocolitis.

Physical examination revealed a superficial, indurated, reddened area 8 cm. in diameter with its center over the right fifth costal cartilage. The skin had an "orange peel" appearance and no fluctuation was present. There was mild tenderness but no local heat. The temperature, pulse and respirations were normal. The general appearance was that of chronic, low-grade infection without abscess forma-

tion. A roentgenogram of the chest showed minimal fibrosis of the right pulmonary apex. Films made with a technic to demonstrate costal detail revealed no evidence of either neoplasm or infection.

The first diagnostic impression was tuberculous infection of the thoracic wall, with the cartilage as a focus. However, a malignant tumor was considered and, therefore, under local anesthesia, a small ellipse of skin and subcutaneous tissue was removed for examination. Microscopically this tissue showed only "slight chronic inflammation, but nothing specific." Since there were no signs of toxicity and no evidence of fluctuation, conservative treatment was first advised. A series of treatments with ultraviolet light over a period of one week was followed by some improvement, but very shortly the pain increased and the center of the indurated region became fluctuant. The temperature rose to 101° F., and incision and drainage seemed necessary.

On April 6, 1943, under nitrous oxide anesthesia, a transverse incision was made over the fluctuant area roughly parallel to the fifth cartilage. Twenty cubic centimeters of thick yellow pus were encountered just beneath the subcutaneous tissue. The pyogenic cavity was lined with granulations grossly resembling tuberculous tissue. A sinus led to the fifth cartilage. On exploration, this cartilage and the chondrosternal junction were found to be diseased and were removed. The granulations of the pyogenic pocket were curetted and all grossly infected tissue removed. The wound was packed open with vaseline gauze. Culture of the pus revealed the presence of *S. cholerae suis* (Kunzendorf var.). All attempts to isolate the tubercle bacillus, including inoculation of a guinea pig, were negative. Microscopic examination of the tissue revealed only "chronic granulomatous inflammation with no evidence of tuberculosis."

The patient's convalescence was uneventful and the wound healed rapidly by relatively clean granulation tissue. However, persistent drainage from a sinus leading beneath the inferior flap necessitated a second exploration six weeks later. In spite of the fact that careful examination of the adjacent cartilages at the first operation had shown no obvious involvement, the sixth and seventh cartilages were now found to be infected. These were resected and again the wound was packed open. *S. cholerae suis* was again cultivated from the pus. Healing by second intention was rapid, until only a small dimple of granulation tissue remained. Several times epithelium covered this small defect but each time a minute accumulation of subepithelial pus would necessitate incision. Finally superficial roentgen therapy was used and complete, firm healing resulted promptly. Six months after the original drainage the wound was entirely healed and has remained so.

### SUMMARY

Five case reports of rare thoracic complications of typhoid and *Salmonella* infections have been presented. Two of these were cases of costal chondritis and three were cases of empyema. All except one, an empyema which terminated fatally, were successfully treated surgically.

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# A STUDY OF ONE HUNDRED CASES WITH A POSITIVE COCCIDIOIDIN SKIN TEST \*

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LATE in 1942 it became apparent to the members of the pulmonary section of an Army General Hospital which serves the southwestern part of the United States that the number of cases of so-called minimal tuberculosis was increasing. It was decided to make intracutaneous tests on all individuals with suspicious lung lesions, not only with tuberculin but also with coccidioidin. One or more coccidioidin intracutaneous tests were made on 372 patients. One hundred twenty-five of these had a positive coccidioidin test. One hundred selected cases who had a positive coccidioidin test and residual roentgenographic findings in the lungs were chosen for study. Their analysis forms the basis for this report. Aside from four fatal cases the remainder were under observation for at least three months.

The disease coccidioidomycosis has been repeatedly described in the literature.<sup>1, 2, 3, 4, 5, 6, 7, 8, 9</sup> For the purpose of this study, a brief summary of coccidioidomycosis is given. The earliest lesions of coccidioidomycosis have not been observed in man but can be surmised from studies on animals.<sup>10, 11</sup> The disease is caused by the fungus *Coccidioides immitis*. The organism is found in the soil of certain arid regions. It has also been isolated from a number of wild rodents. In this country it is found chiefly in parts of central and southern California, Arizona, New Mexico, and West Texas.<sup>12, 13, 14, 15, 16</sup> The organism is diphasic.<sup>17, 18, 19</sup> In the soil and on culture media it occurs in the form of hyphae with chlamydo-spores. This is the infective form of the fungus. In animal tissue the organism occurs as a spherule with a doubly refractile wall. The spherules vary in size from 10 to 60 micra. The spherules multiply by endosporulation and gain release to the tissues when the mother cell ruptures.

The usual pathological lesion is an infectious granuloma.<sup>20</sup> The following is an autopsy protocol on the lungs of one of our patients. The findings in the patients who died are essentially similar and one case presents the picture for all.

"The pleura at the right apex is slightly thickened and is overlaid by fibrous tags. All lobes of both lungs are moderately firm and exhibit decreased crepitus. On palpation all lobes have a slightly 'shotty' consistency. The cut surfaces are mottled purplish-pink and slightly bloody, and on close inspection in oblique light numerous pinhead sized gray, slightly raised, miliary lesions can be seen throughout all lobes. No areas of frank consolidation or cavitation are present. The bronchi and pulmonary vessels appear normal. The lymph nodes at the hilum are moderately

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enlarged. The capsules are thickened, and the cut surfaces display large, irregular, soft, greenish-gray areas.

"(Microscopic Examination) Scattered through the lungs are innumerable small granulomatous lesions each occupying the space of two to five alveoli. These separate lesions vary in structure and age. The most typical ones show a central necrotic focus with one or more small multinucleated giant cells and characteristic coccidioides organisms. The periphery of the granulomata is occupied by various types of mononuclear elements. There are numerous variations upon this picture. What are apparently the earliest stages consist of an accumulation of mononuclear cells mingled with polymorphonuclear leukocytes within a single alveolus whose walls are well preserved. Parasites may or may not be present among the infiltrating cells. Giant cells are absent in these early foci. There are small conglomerations of such lesions with well preserved alveolar septa between them. Still later the alveolar septa are destroyed. A slight amount of diffuse fibrosis appears while necrotic centers and giant cells make their appearance. The most mature lesions appear with abundant fibrosis and a partial irregular encapsulation. In addition to these lesions there are moderate amounts of protein coagulum within some alveoli together with many red cells and numerous large macrophages with vacuolated cytoplasm and small amounts of pigment. The alveolar septa are in general moderately thickened and show considerable congestion. The alveolar walls are in general surprisingly well preserved. No large abscesses or cavitations are present."

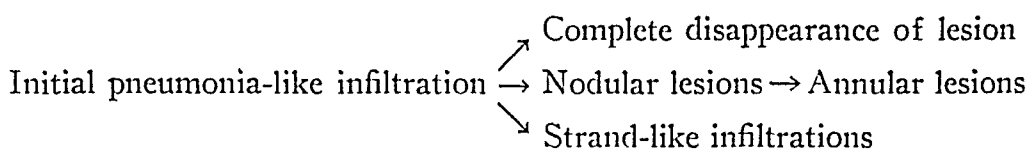
The organism gains entrance into the body through the inhalation of infected dust, or rarely through a lesion in the skin. The vast majority of infections are mild, self-limited, and involve the lung and associated mediastinal lymph nodes.

As resistance to the disease develops, antibodies appear in the blood and the lesion heals. Frequently the lesion disappears, but occasionally fibrosis sets in and a rounded or linear scar is left. In such instances a solid immunity to the disease results. Reinfection with coccidioides does not occur. In an exceptional case an abscess may form in the lung or pleura. Such a lesion may eventually heal by absorption and fibrosis, but on the other hand it may break down and the contents be discharged through a bronchus. In the latter instance, the organisms may appear in the sputum for months or years, but apparently do not cause secondary lesions. Very rarely, owing to the severity of the initial infection or to the poor resistance of the individual (dark skinned races mostly), the infection is not limited to the lung and associated lymph nodes but gains entrance into the blood stream. Following inoculation into the blood stream, no organ or tissue of the body is immune. Many of these individuals die. A few develop enough immunity to the disease to survive, although granulomata continue to make their appearance throughout the body and are slowly absorbed or form chronic abscesses. Coccidioidomycosis mimics tuberculosis very closely. However, it is important to note that superinfection type (adult type) of pulmonary tuberculosis is not characterized by hilar or mediastinal adenopathy as is coccidioidomycosis of the lungs.

Roentgenographic studies in human cases tend to corroborate the above sequence of events.<sup>21, 22</sup> From a roentgenographic standpoint<sup>9</sup> the initial lesion in coccidioidomycosis is a pneumonia-like area of increased density



in the lung of variable size and location. Shortly thereafter one or both hilar regions usually show evidence of lymph node enlargement. If the disease does not disseminate, the pneumonia-like area will regress in a period of weeks or months. Frequently this initial lesion is confused with so-called atypical or virus pneumonia. As healing takes place the lesion may disappear or remain unchanged. If not, a rounded nodular dense area or strand-like area which often extends into the hilum is left. Occasionally the nodular lesions are seen to develop a central area of lesser density which gives the lesion the appearance of a cavity. The situation can be represented schematically as follows:



The most interesting and difficult problem presented by our cases is the individual who shows a very small, soft area of increased density somewhere in the lung parenchyma on roentgen examination, but is otherwise well. The lesion usually has to be differentiated from tuberculosis, although the residuals of a pneumonitis (fibrosis, healed septic abscess, bronchitis, and bronchiectasis), Boeck's sarcoid, and metastatic malignancy may cause confusion. In an effort to establish a diagnosis in these cases particular attention was paid to the history, including the relevant facts concerning activities in areas endemic for coccidioides, the physical examination, skin tests for coccidioidin and tuberculin, blood count, urinalysis, blood Kahn and Wassermann tests, sedimentation rate, sputum, study of blood for coccidioidal antibodies, and roentgenographic examination of the chest. The following is a summary of the pertinent findings:

*History.* Fifty-two patients gave a history of pulmonary symptoms following their entrance into the desert. The typical history was that of an acute illness with fever, mild chills, cough, occasional slight hemoptysis, small amounts of mucoid sputum, and chest pain. Malaise was a frequent finding and in combination with the chest pain usually persisted. These symptoms are not characteristic of any disease but when they are found in an individual shortly after his entrance into the desert they raise the suspicion of a coccidioidal infection.

*Physical Examination.* The physical examination of the chest in most instances was entirely negative. Pleurisy, pleurisy with effusion, and pneumonitis, all secondary to a coccidioidal infection, can usually be found by physical examination. In comparison with the number of individuals who show pulmonary lesions by roentgenogram they form a small group, as only eight patients presented definite findings. From this it was felt that an evaluation of the lungs cannot be made without a roentgenogram. Four patients had skin manifestations. These proved to be coccidioidal granulomata and in three the granulomata had broken down into abscesses.

*Skin Tests.* Until November 1943 the Vollmer patch test was extensively used to rule out tuberculosis. At this time it was decided to make intracutaneous tests on all individuals giving a negative patch test with tuberculin, purified protein derivative, second strength. This strength contains 0.005 mg. of purified protein derivative per dose. We found a certain percentage of individuals who gave a positive reaction to purified protein derivative who were negative to the Vollmer patch test. This is summarized in table 1. In man, infection with *Coccidioides immitis* produces a sensitiv-

TABLE I

Total Number of Vollmer Patch Tests		
Positive.....	131	55%
Negative.....	107	45%
Total Number of Purified Protein Derivative, Second Strength, 0.005 mg. per Dose, Skin Tests		
Positive.....	113	72%
Negative.....	43	28%
Negative Vollmer Patch Tests Checked by Purified Protein Derivative, Second Strength		
Positive.....	6	
Negative.....	5	

Significance of Difference Between Vollmer Test and PPD No. 2:

Vollmer positive in 55%  
 PPD No. 2 positive in 72%  
 Difference 17%

Standard deviation of difference,  $\sqrt{\frac{131 \times 107}{238} \frac{112 \times 43}{155}} = .0483$

Delta over sigma delta,  $.17 / .0483 = 3.5$

The probability of the occurrence of a deviation of  $3\frac{1}{2}$  sigma is .0465, or in other words the odds against such an occurrence being a chance fluctuation in sampling is 2149 to 1 (if the conditions of simple sampling are fulfilled).

ity to coccidioidin which is essentially similar to the sensitivity produced to tuberculin by infection with the tubercle bacillus. With proper precautions the coccidioidin skin test is a very reliable procedure.<sup>12, 23, 24, 25, 26, 27, 28</sup>

The coccidioidin for skin testing was obtained from Dr. Charles E. Smith of the Department of Public Health, Stanford University Medical School. Dr. Smith dispenses coccidioidin in a concentrated form. We use this material in a 1:100 dilution with normal saline. No preservative is added and the diluted material is kept in the icebox. Over a period of a year and a half, different batches of the diluted coccidioidin have been frequently checked by testing known negative and positive reactors.

Of 372 patients tested seven, or 1.8 per cent, had an equivocal skin reaction. By equivocal is meant a reaction in which the area of redness and swelling was between 0.2 cm. and 0.5 cm. in diameter, faintly red, with little or no swelling. Subsequent skin tests on three of these patients were negative. The other four became definitely positive. These seven patients had all been in areas endemic for coccidioides. An inconclusive skin test must

be repeated. We chose different areas of skin for later tests. With repetition we were able in every instance to establish a reliable result. By this is meant that a positive skin test was not found in any individual who had not been in areas endemic for coccidioides. Six individuals had a severe reaction from the coccidioidin. The severe reactions were similar to those occasionally seen with tuberculin, although the tendency to ulcerate is not so great. In no patient was the reaction alarming, but there were redness and swelling of the entire anterior forearm, lymphangitis, and lymphadenitis as well as a constitutional reaction, with fever up to 101° or 102° F. A few individuals with negative or equivocal reactions were tested many times. In no instance did we see a sensitivity develop to the subcutaneous injection of coccidioidin. Of the 100 cases reported, 72 were tested more than once and were repeatedly positive. All of the equivocal skin tests and the majority of the definitely positive were checked by one of us (H. D. C.) All of the patients had a positive coccidioidin skin test at some time in the course of their disease although in two instances the test became negative as the patient became desperately ill with the disseminating form of the disease. The same type of anergic reaction is seen in tuberculosis of severe degree.

*Blood Count and Urinalysis.* Blood counts and urinalyses were of no aid in differential diagnosis.

*Blood Kahn and Wassermann Tests.* Although it is not pertinent to this study, it was noted that in five individuals, seriously ill with a coccidioidal infection, the blood Kahn and Wassermann reactions or both changed from negative to positive and back to negative again when the individual improved. There was no suspicion of a syphilitic infection in these individuals.

*Sedimentation Rate.* The sedimentation rate is elevated during active stages of the disease. In this series of cases the sedimentation rate was repeatedly normal in 61 patients.

*Sputum.* *Coccidioides immitis* was obtained by culture of the sputum in nine patients. These individuals were all seriously ill with the disease. Four of the nine patients died. In two patients, coccidioides in spherule form was seen on smear of the sputum but was not obtained on culture. We do not consider a positive smear with a negative culture for coccidioides definitely indicative of infection. It is not unusual, however, to find the double contoured spherules of coccidioides by smear in pus or spinal fluid which on culture is sterile. On June 2, 1943, one of our patients had spherules in his spinal fluid by smear, and coccidioides was obtained by culture. On June 12, 1943, spherules were again seen by smear of spinal fluid which on culture showed no growth. The patient, incidentally, made a good recovery, and examination in October of 1943\* was essentially negative except for minimal lung changes. Fifty-six patients had no sputum in any quantity. Two or more gastric lavages done on these patients before breakfast were completely negative for coccidioides by smear and culture. In our

\* Patient left the Veterans' Facility without permission and did not return.

experience it is extremely difficult to recover the organism from the sputum of patients with coccidioides except in the early, acute stages of the disease or in the disseminating form of the disease. In addition to the search for *Coccidioides immitis* all sputa and gastric contents were examined for acid fast organisms. Two patients with upper lobe lesions and positive skin tests for coccidioidin and tuberculin were found to have acid fast organisms in their sputa. They are not included in this series of 100 cases but they do emphasize the necessity for a careful search for the tubercle bacillus under the circumstances.

*Antibodies in the Blood.* Complement fixation and precipitin antibodies for coccidioides may be found in the blood, spinal fluid, and chest fluid when present, in the active stages of the disease.<sup>6</sup> Any given lesion of the chest found by roentgenographic examination and meeting certain criteria which will be more fully described below may be presumed to be due to coccidioidal infection if antibodies are found. This is due to the fact that in the vast majority of instances coccidioidal infection has its origin in the lungs. This initial infection can generally be visualized by roentgenogram at least as long as antibodies are to be found. Nine patients had complement fixation or precipitin antibodies in the blood.\* This figure does not represent a true picture of the incidence of antibodies in the blood because specimens were not submitted from those patients in whom the fungus was found in the sputum or from the majority of patients whose disease appeared inactive.

*Roentgenographic Findings.* Table 2 presents the cases classified as to

TABLE II

## Tabulation of Residual Lesions

This chart does not tabulate the number of individual cases with specific individual lesions. It shows the number of times that the type of lesion described in the left hand column appeared in the groups of cases presented. One case may have manifested several different types of changes in the same chest at the same time.

Group	A	B	C	D	
Type of Manifestation on Chest Film	Proved (5 Cases)	Positive Coccidioidin Negative PPD2 (15 Cases)	Most Probable (10 Cases)	Those With Positive Coccidioidin and Positive PPD2 or Positive Patch Test (66 Cases)	Total (96 Cases)
Pneumonia- Like Areas	2	—	3	21	26
Hilar Adenopathy	3	7	6	25	41
Nodular	1	6	6	38	51
Annular (Cavity)	2	3	2	14	21
Upper Lobe Infiltrations	—	—	1	16	17

\*The examinations were made in the laboratory of Dr. Charles E. Smith, Dept. of Public Health, Stanford University Medical School, San Francisco, California.

the major type of roentgenographic changes exhibited and presents a combination of other clinical manifestations which aid in proving the diagnosis. The roentgenographic lesions in the lungs of 34 patients were considered to be due to coccidioidomycosis. Of these, group one, which consisted of nine cases, includes the autopsy cases. These patients had the organism isolated from the sputum. The second group, 15 in number, presented a negative reaction to the tuberculin skin test using purified protein derivative, second strength. The third group has certain outstanding findings. These are mild

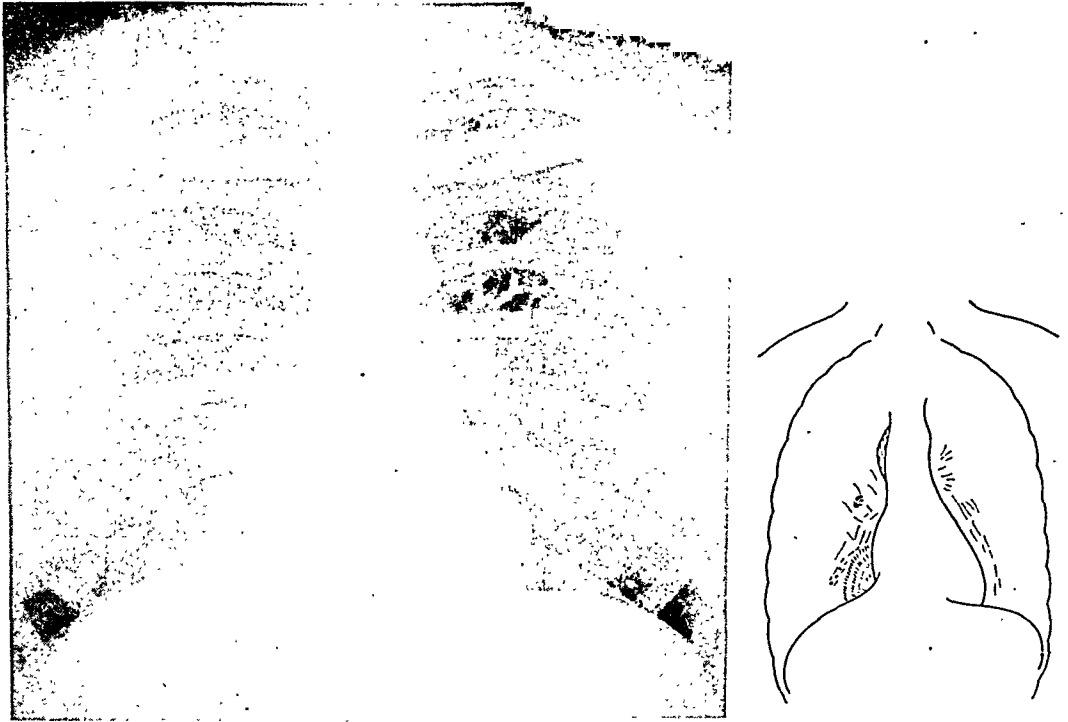


FIG. 1. Entered endemic area in May 1943. Onset of cough, dyspnea and hemoptysis early in September 1943. Coccidioidin became positive October 13, 1943, and has been positive on two tests since. Tuberculin patch test is positive. A pneumonia-like area is noted extending outward from the right cardio-phrenic angle on first observation. A slight convexity in the right upper hilar region beyond the usual course of the descending aorta is noted interpreted as a hilar node enlargement. Figure 1-A an examination 5 months following the first shows the area to have contracted to a roughly round granular appearing area of rather discrete density increase. The prominence in the upper hilum has disappeared. Intensification persists between the hilar region and the round area in the right cardio-phrenic angle. This lesion is classified as a large nodular, single type of lesion.

antibody formation in the blood, the presence of fungi in a sputum examination by smear only, or the isolation of the organism from lesions other than the lungs. This group is composed of 10 cases. The other 66 cases are those individuals who in addition to a positive coccidioidin skin test, gave a positive reaction to some type of tuberculin skin test. In 36 of the 66 cases the lesions were thought to be due to coccidioidomycosis largely because of the presence of an associated hilar adenopathy or rapid regression of the lesion. This opinion was strengthened by comparing these lesions with

those of the 34 patients mentioned above. Whenever possible, former chest films were obtained. Some of these films show the development of the chest lesions as described. Examination of previous chest films frequently gives further valuable information and should always be done if such films are available. We have felt that a lung lesion, absent before but present some time after an individual was on the desert, was probably due to coccidioidomycosis even though the tuberculin skin test is positive.

The majority of the roentgenographic findings may be grouped under five major types as indicated in table 2.

1. *Pneumonia-Like Infiltrations* (figures 1 and 1-A). These areas are

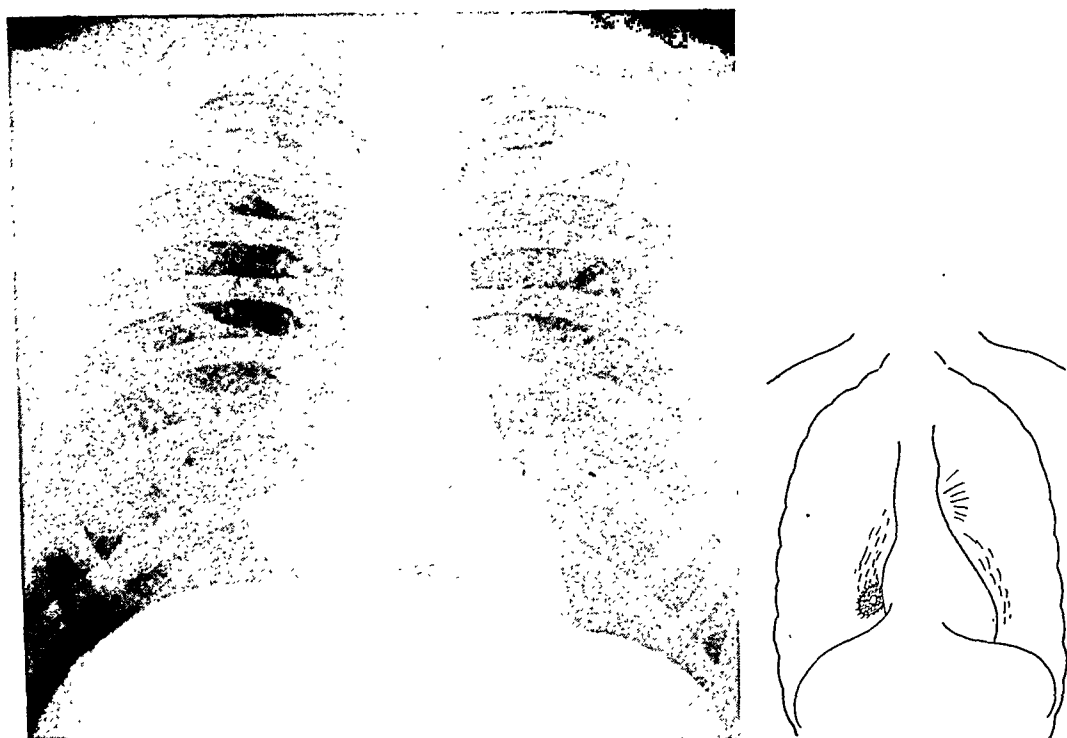


FIG. 1-A.

patchy infiltrations, centrally or peripherally situated in a portion of, or an entire lobe of a lung. The area has a variable density increase but on close examination the primary appearance is that of a group of tiny discrete nodulations intermingling with a rather soft density increase. This manifestation may be accompanied by various forms of local or generalized pleural reaction. On serial observation over a period of time the areas have frequently been noted to develop into various types of lesions such as the nodular, annular, strand-like or different combinations of all three.

2. *Tracheo-Bronchial, Mediastinal, or Hilar Adenopathy or a Combination of All* (figures 2 and 3). We have been impressed by the fact that at some time during the course of the disease changes occur in hilar shadows

of the lung which are either suggestive of, or positively identified as, significant lymph node enlargement. We believe the presence of mediastinal or hilar adenopathy to be a characteristic of pulmonary coccidioidomycosis at some time during the evolution of the pathologic process in significant infections.\* These hilar shadows interpreted as enlarged lymph nodes vary in size from only a slight convexity in the lung root to large nodes as pre-

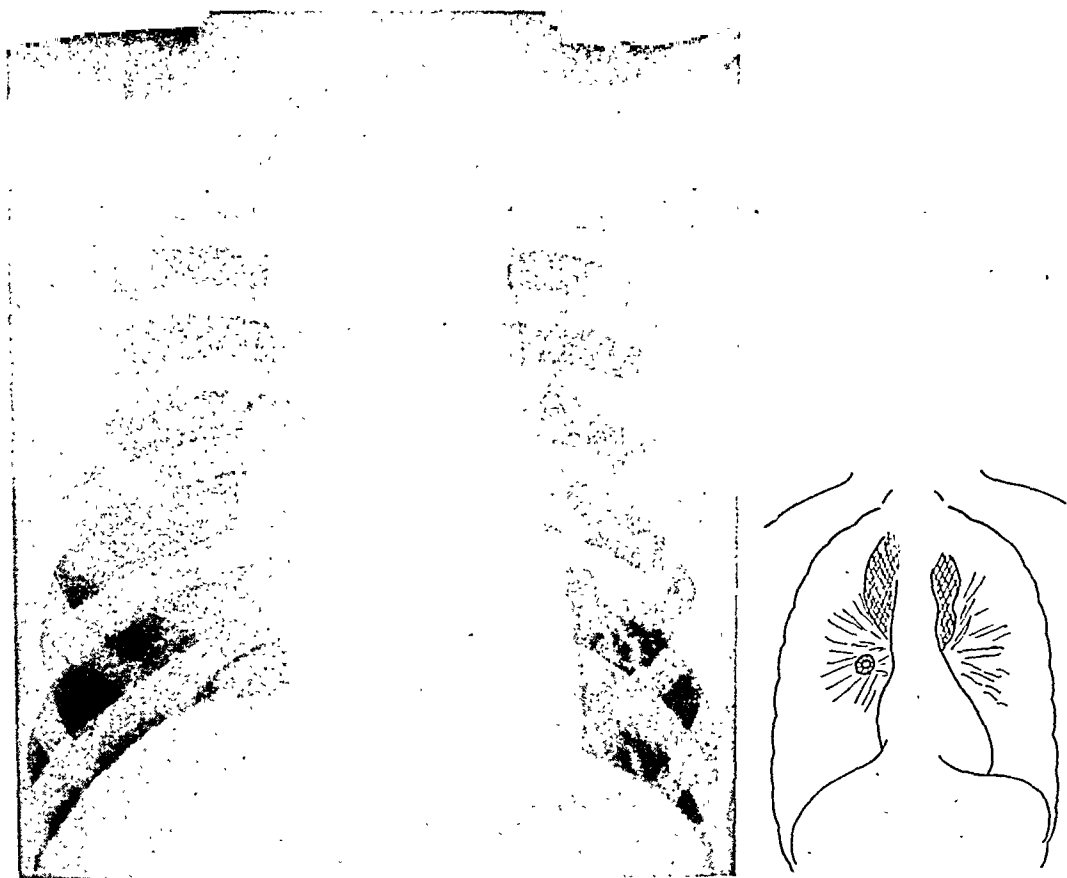


FIG. 2. First hospitalized December 22, 1943, after having been in endemic area for a period of 14 months. Presenting complaint was pain in center of chest, chills, fever and some cough. The coccidioides organism was positively identified in this patient's sputum approximately 2 months after the onset. Marked hilar or mediastinal adenopathy is noted. This adenopathy occurred to such extreme enlargement within a period of 14 days. The faintly visible lesion in the right hilar region is a type which may be easily overlooked unless careful search for it is made.

sented in figure 2. They often persist over a period of months. One patient (figure 3) had suggestive evidence of hilar adenopathy and a lung lesion that was thought to be due to coccidioidomycosis. In addition, he had chronic bronchitis which was later shown actually to be bronchiectasis. He

\*The actual percentage of definite residual hilar adenopathy is 45. The per cent of definite or suggestive hilar adenopathy occurring early in the disease cannot be ascertained. By the time the importance of hilar adenopathy was appreciated many of the roentgenograms were transferred. However, the clinical impression of the authors from their studies is clearcut that hilar adenopathy is found at some stage of the disease process.

died from a brain abscess and at autopsy the hilar nodes were found to be slightly enlarged as a result of chronic inflammation. No coccidioidal granulomata were found in the nodes or in the lungs even though he had a positive coccidioidin skin test. In this instance the hilar adenopathy was not significant.

Hilar adenopathy due to coccidioides can occur with no demonstrable parenchymal lesion. If serial roentgenograms have been made on these

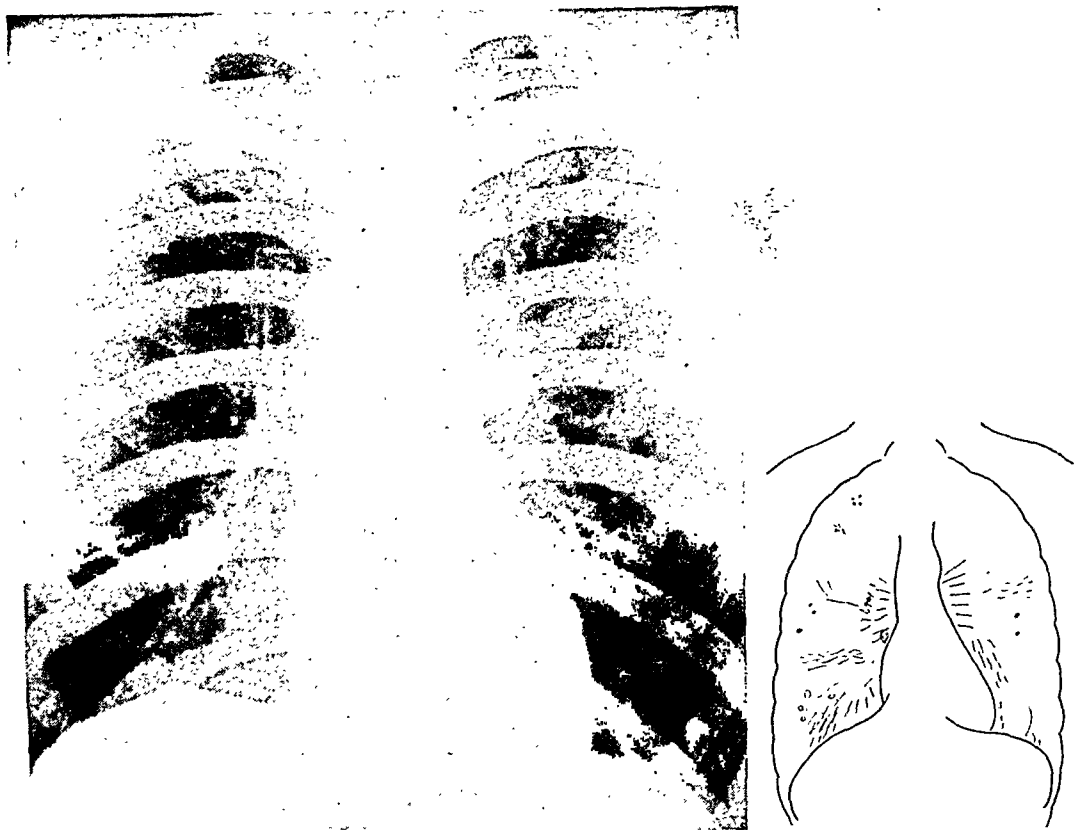


FIG. 3. This 22 year old white male entered the hospital on August 12, 1943, from Florence, Arizona, where he had been stationed since June 1943. Patient was on limited service because of chronic bronchitis. Recently had had weakness, easy fatigue, increase in cough, loss of weight, chills, sweating, small amount of yellow sputum, and pain in chest. Coccidioidin and tuberculin skin tests both positive. Bronchogram on September 15 showed bilateral tubular bronchiectasis. Following a cold, he developed right sided empyema, brain abscess, and died November 15, 1943. Autopsy confirmed these findings and showed presence of small hilar nodes without any evidence of coccidioides.

patients from the beginning of the disease lung changes can usually be demonstrated. Two of our patients who early showed lung lesions with marked enlargement of the hilar nodes were left with only the hilar adenopathy. One other patient with marked hilar adenopathy did not show a lung lesion. When this occurs node enlargement due to Boeck's sarcoid and lymphoblastoma have to be differentiated. We gave this individual the first course of the usual roentgen-ray treatment for lymphoblastoma. The



nodes did not diminish in size so that we were inclined to consider the lesion as due to coccidioidomycosis. This was especially true as there was no further evidence which indicated the presence of Boeck's sarcoid, such as the rounded areas of lesser density seen in the roentgenogram of the hands and feet, the increased serum protein, the presence of the typical granulomata of sarcoid in a biopsy of a superficial gland, or the iritis, parotitis, facial nerve syndrome.

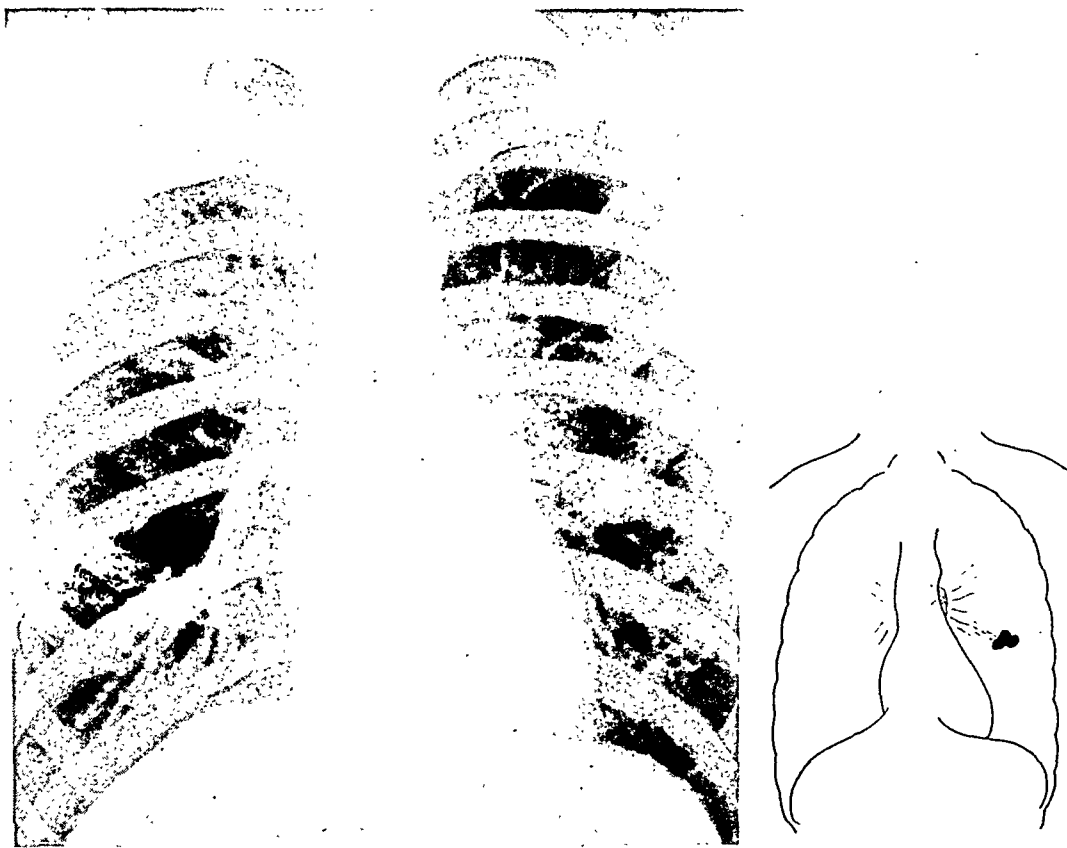


FIG. 4. Entered endemic area for coccidioidomycosis at least 6 months prior to application for Officer's Candidate School where an abnormal density was found in left lung. Patient was transferred to present hospital October 22, 1943, with a diagnosis of tuberculosis, pulmonary, left lower lobe, active, acute. On examination at this station all findings except that shown in above roentgen-ray examination were negative except a positive skin test for coccidioidomycosis and the patient had negative patch and PPD, second strength, tuberculin test.

3. *Discrete Nodular Type* (figures 4 and 5). This lesion is a round or oval area of increased density situated in the lung field usually at the periphery and predominantly in the middle and upper lung fields. The density of these areas is somewhat less than calcium and greater than the usual vascular density in the hilum of the lung. The lesions are discrete and rather sharply demarcated. They may be single or multiple.

Some of these nodular lesions have been observed to change over a period of time to ones having a central area of lessened density resembling

cavity or abscess formation. Within another lapse of time they may resume their nodular configuration and homogeneous density. The size of these areas varies from 2 to 3 mm. up to the largest observed in this series, which measures 3.5 cm. in diameter. Smith<sup>9</sup> has noted that these lesions occasionally may calcify. One of our patients who apparently contracted his disease many years previously, while a resident in the San Joaquin Valley of California, showed this condition (figure 6).

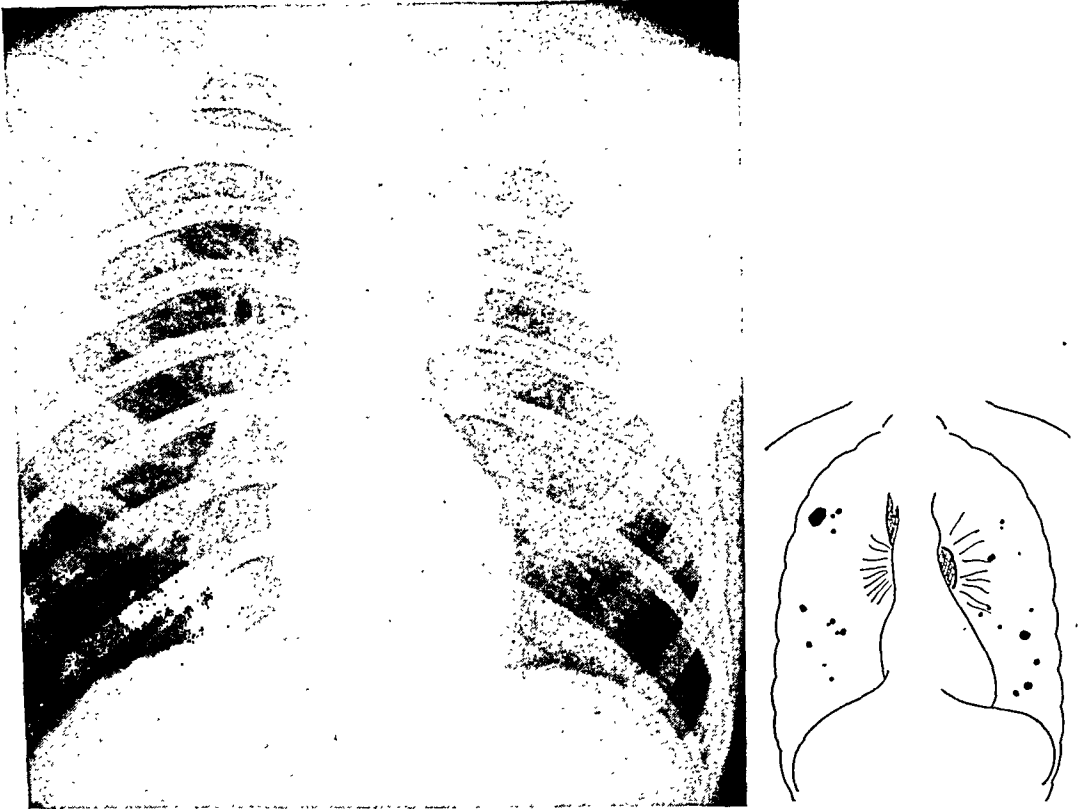


FIG. 5. Entered endemic area April 21, 1943. During September he began to tire easily, had backache and headaches. Entered local hospital October 21, 1943, transferred October 31, 1943, at which time tuberculin patch test was negative. Coccidioidin skin test was positive. No significant physical findings referable to the chest. The multiple, scattered, variable sized, round, discrete nodular areas of greater density are noted. These areas resemble the occasional so-called grape-like shadow associated with tuberculous findings. Observation of this patient's chest over a period of four months shows that these nodular areas became less dense (faded) and smaller. The patient was subsequently returned to full duty. Both single and multiple nodular types of this lesion have been observed, in sizes varying from a few mm. up to the largest, approximately 3 cm. in diameter.

4. *Annular Shadows* (Cavities, figures 7 and 7A). The predominant annular shadows observed in this series are areas of annular configuration having a relatively thick wall. As described under the nodular type these areas may change from time to time but always have a relatively thick wall which closely resembles a zone of inflammatory reaction about a focus of necrosis. There is no evidence of tissue reaction beyond the total area of involvement.

A thin-walled type of cavity has been conspicuous by its rarity in this series of cases. The one outstanding case presenting this finding is seen in figure 8. This closely resembles the pneumatocoele-like shadow described by Carter <sup>21</sup> and the thin-walled cavity described by Winn.<sup>20</sup>

5. *Upper Lobe Infiltrations* (figures 9 and 9A). This type of infiltration is confined to the upper lung field where a suggestively fine granular or poorly defined fuzzy cloudiness is present with extension of linear markings



FIG. 6. Patient lived most of his life in the San Joaquin Valley of California. Chest films were made in 1942 and in 1944 and are essentially the same. The tuberculin skin test, PPD, second strength, was repeatedly negative. Coccidioidin skin test was positive. All of the nodular type lesions show internal calcifications.

into the hilum. In some cases, on close examination of these areas, very small nodular formations may be observed with an occasional area suggesting a very small cavitation.

*Roentgen-Ray Lesions in Autopsied Cases.* The different types of roentgen-ray manifestations above described and demonstrated in figures 1, 2, 4, 5, 7, 8, 9 inclusive were seen in the four patients who died and on whom autopsies were performed. All four of these cases presented roentgen-ray

findings in the chest which suggested a diffuse inflammatory process as the essential gross finding. Additional detailed evidence was as follows:

One case presented diffuse miliary nodular lesions with fuzzy linear intensification throughout both lung fields when first seen. During two months' observation these miliary lesions were seen to progress in both size and number until on an examination just prior to death there were blotchy areas present resembling confluent bronchopneumonia. These blotchy areas appeared to be a coalescence of some of

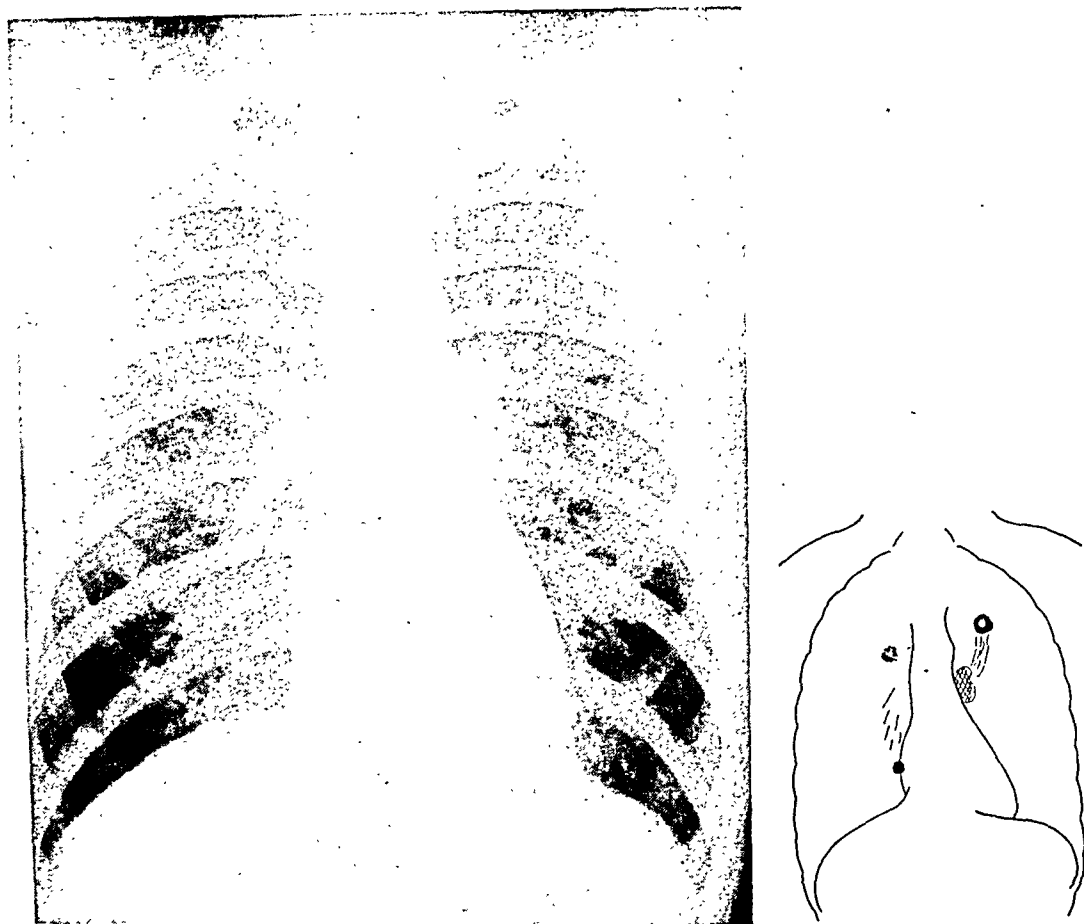


FIG. 7. Time of entrance into endemic area not definitely known. Entered Hospital in Arizona May 15, 1943. No symptomatic history. Has positive coccidioidin skin test. The round cavity or abscess-like shadow in the left upper lung field is noted. Attention is called to the wall thickness of this abscess or cavity compared to its total size; also to the comparative radiolucency of its central portion and the sharply demarcated peripheral border.

the nodular areas. The gross appearance of the cut surface following autopsy showed these areas to be round pneumonia-like areas of infiltration, many of which were lying close together. All four cases (figure 1) presented blotchy areas of increased density in the lung fields which resembled bronchopneumonic involvement.

Two cases presented definite discrete oval densities in the lung root shadows which were interpreted as and later demonstrated to be enlarged nodes in the lung root. All cases presented exaggerated hilar markings, far more than seen in the usual inflammations of pulmonary structures. The autopsies of the four cases re-

vealed enlarged hilar lymph nodes in each patient. The microscopic examination showed the nodes to be involved by coccidioidal granulomata.

One case, just prior to death, presented evidence of a beginning effusion between the right upper and middle lobes. At autopsy a right hydrothorax was present.

### DISCUSSION

It is evident that a great many individuals who have been in the southwestern United States show a positive reaction to the coccidioidin skin test.

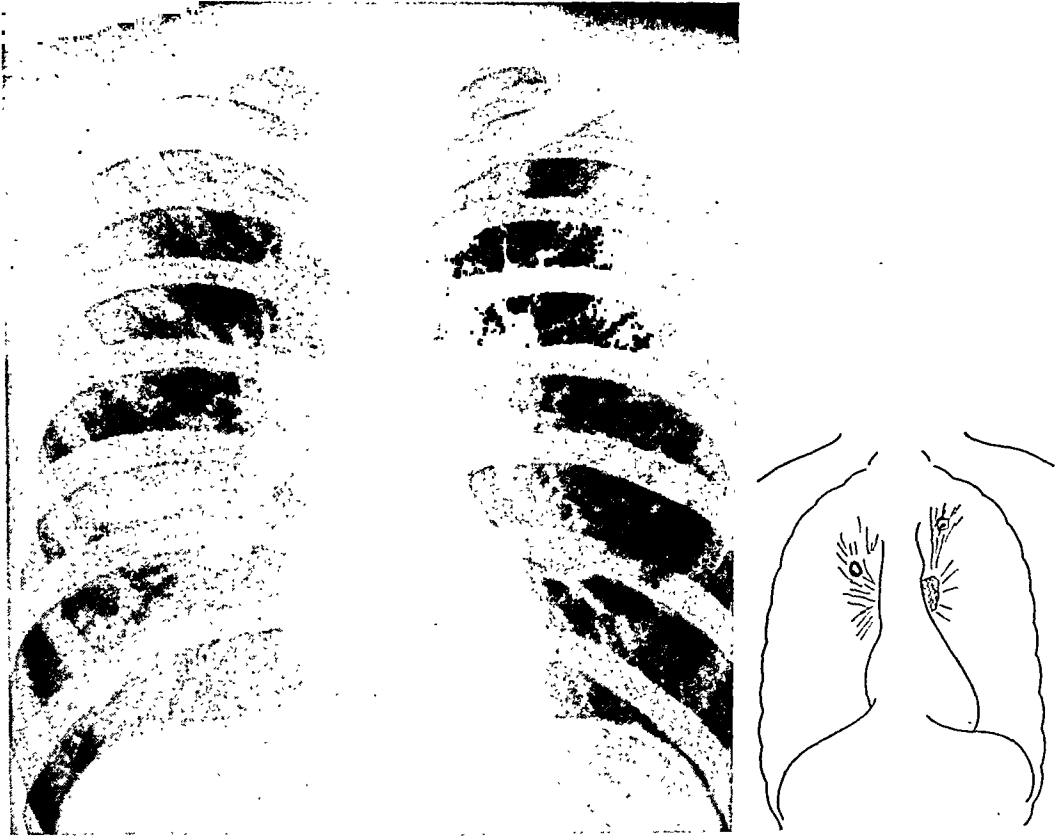


FIG. 7-A. The tendency for the thick walled annular shadow in the left upper lobe to assume a nodular type of lesion can be noted in this instance in a period of three months.

It is also apparent that of these individuals a sizeable percentage, the approximate number unknown, will exhibit roentgenographically persistent areas of increased density in the lungs of variable size and shape. These abnormal shadows probably will most often be considered to be tuberculous. If the lesion should prove to be tuberculous, it is likely to be potentially dangerous and would require supervision for a period of months or years in order to determine activity. If due to a coccidioidal infection, it is a relatively easy matter to determine the activity of the lesion which, if inactive, can be disregarded as a cause of future illness or disability. In certain in-

stances, much less numerous than with tuberculosis, other conditions will have to be distinguished from coccidioidomycosis.

The usual roentgenographic appearance of the initial focus or foci of pulmonary coccidioidomycosis is that of pneumonic infiltration. As the lesion changes, stabilizes, and heals, the residua in the lung fields assume such shapes as nodular, annular, linear, or a combination of all of these lesions. We have considered these lesions in individuals who have a positive coccidioidin skin test and negative tuberculin skin test to be due to coccidioidomycosis. If both skin tests are positive, it is not possible to tell with cer-

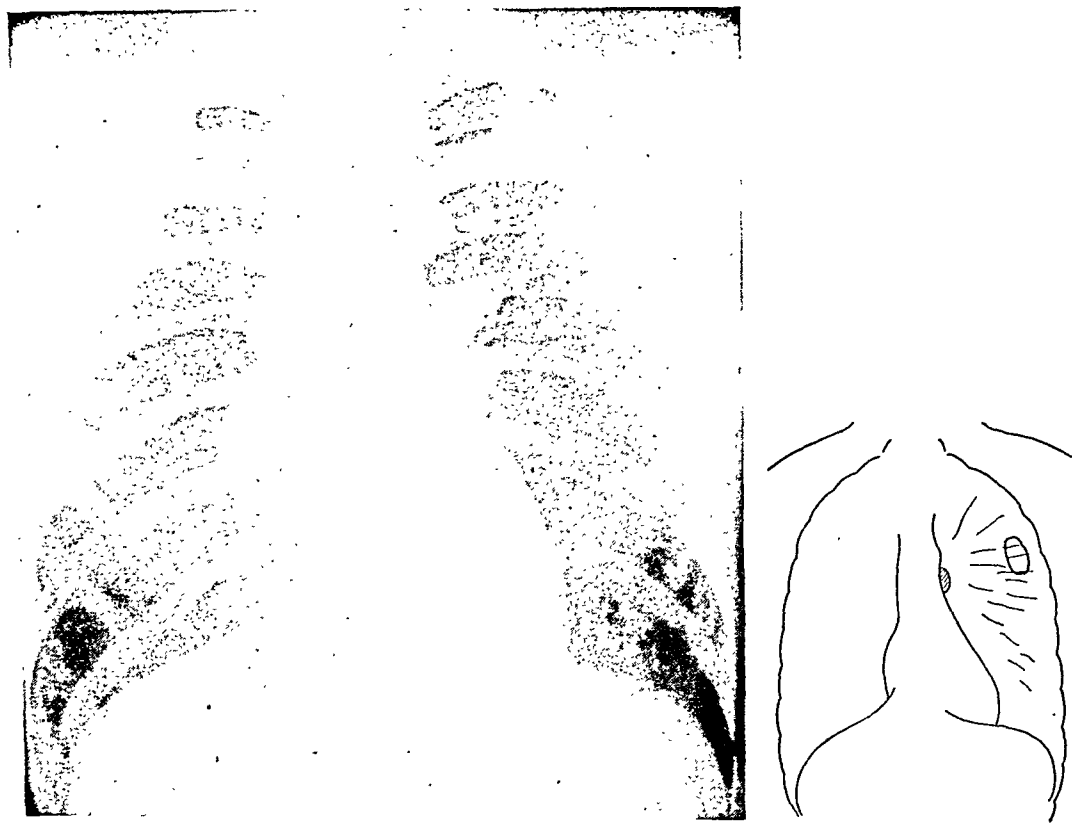


FIG. 8. The thin walled type of cavity (pneumatocoele) described by Winn and others has been conspicuous by its rarity in this group of cases as it has been observed only in two instances.

tainty the nature of the pulmonary lesions. However, some time during the course of the disease most cases of coccidioidomycosis show either definite or suggestive hilar adenopathy. The superinfection type (adult type) of tuberculosis is not associated with hilar adenopathy and although it is not possible to say definitely that a lung lesion associated with hilar adenopathy is due to coccidioidomycosis, the evidence favors such a diagnosis. The other pulmonary lesions that in our experience have occasionally to be differentiated from coccidioidomycosis are: (1) An old pneumonitis with residual scarring. Pneumonitis is frequently part of a bronchiectasis syn-

drome in which there may be nonspecific hilar adenopathy. (2) Boeck's sarcoid. It is seldom that the lesions of this condition, including involvement of the hilar lymph nodes, are limited to the lungs. Other criteria than lung lesions are needed to establish a diagnosis of sarcoid. (3) Metastatic malignant lesions of the lungs can usually be differentiated after a study.

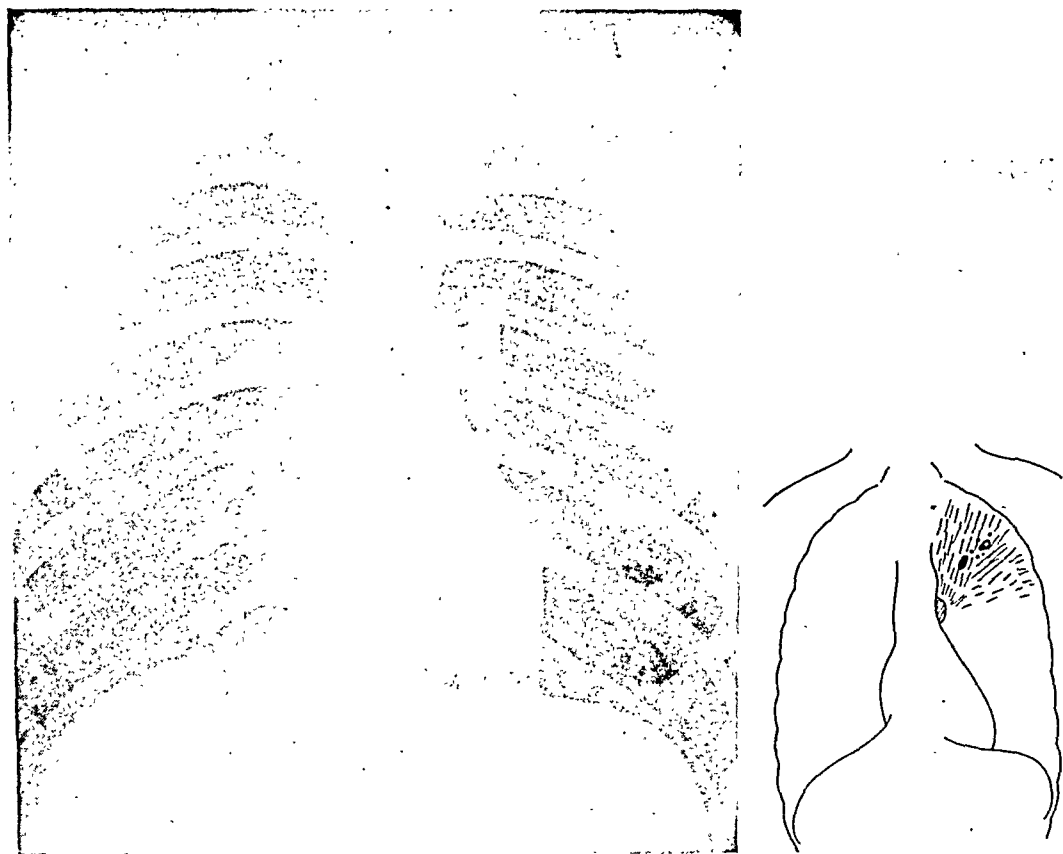


FIG. 9. Patient entered endemic area July 15, 1943. Onset of disease was apparently August 21, 1943, when he began having pain in left anterior mid chest which increased on inspiration with no cough. Physical examination was essentially negative. Skin test for coccidioidomycosis became positive on test November 18, 1943. Tuberculin test PPD No. 2 was negative, Kahn negative. Figure 9 shows an infiltrative process through the left apical region and sub-clavicular region which closely resembles that often seen in the adult type of tuberculosis. The possible identifying features which might make one suspect the presence of coccidioidomycosis are: first, an area which suggests a small thick-walled annular shadow intermingled with numerous round nodular shadows, and secondly the presence of the hilar adenopathy on the left.

This is particularly true of testicular tumor and hypernephroma in which the primary lesions can generally be demonstrated.

#### SUMMARY

1. Three hundred and 72 patients who had spent time in the southwestern United States were tested intracutaneously for coccidioidomycosis. One hundred and 25 of these individuals gave a positive reaction to the skin test.

2. Of the positive reactors, 100 selected cases who showed a pulmonary lesion by roentgenogram during the period of observation were chosen for study. These individuals were also skin tested with tuberculin.

3. The lung lesions of 34 of the selected patients could be classified as coccidioidomycosis. Of the 34 patients nine showed *Coccidioides immitis* organisms in the sputum; 15 had a negative tuberculin skin test; and 10 showed *Coccidioides immitis* in the sputum by smear only, or lesions of coccidioidomycosis elsewhere than in the lungs.

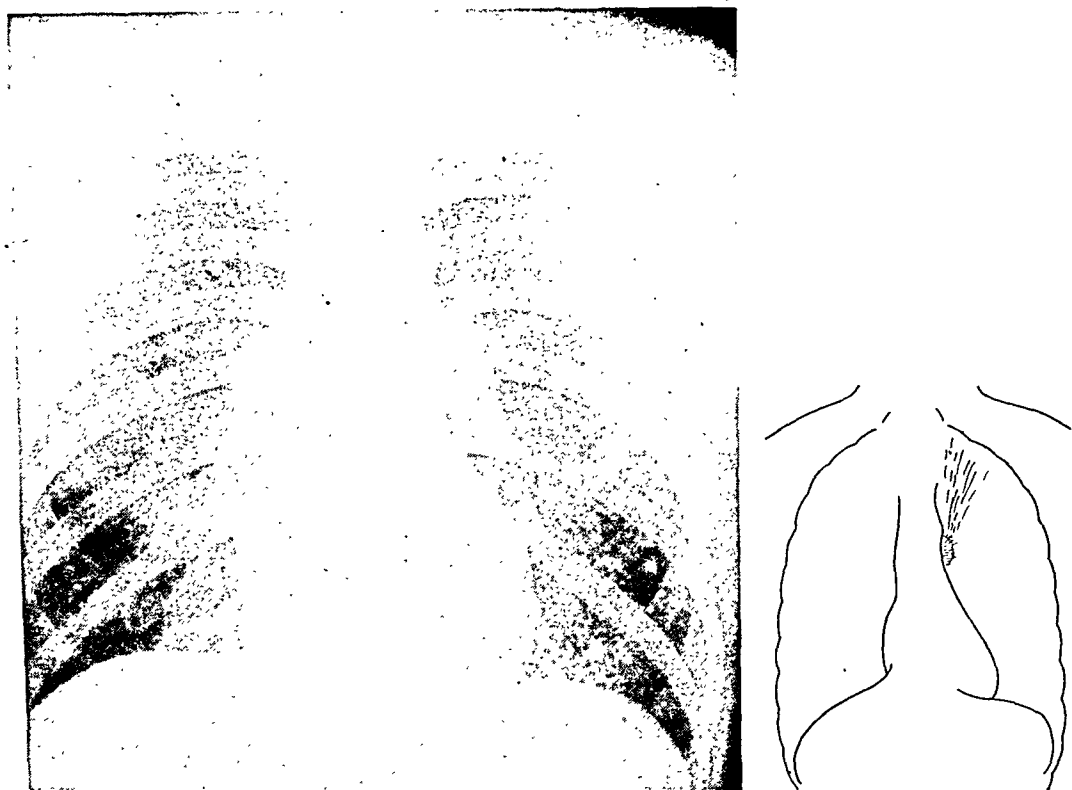


FIG. 9-A. Chest of same individual as in figure 9, approximately two months later with rapid resolution of the infiltrative process previously noted. This finding does not usually occur in tuberculosis. The hilar node persists.

The lung lesions in the remaining 66 patients who had a positive skin test for both coccidioidin and tuberculin were evaluated in the light of the experience with the known positive cases. Although a definite statement cannot be made, yet the evidence indicated that the lesions in 36 of these cases were due to coccidioidomycosis.

4. A pulmonary lesion by roentgenogram in an individual with a positive coccidioidin and tuberculin skin test was considered most likely to be coccidioidomycosis if the lesion was nodular, round, discrete, less than 3.5 cm. in diameter, of a density less than calcium but greater than the usual vascular



density in the hilum of the lung, and associated with suggestive or definite hilar adenopathy.

The authors wish to express their appreciation to Staff Sergeant William Roush and to Private Gaston Matifas for assistance in photographic and diagrammatic presentations.

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# SHORT P-R INTERVAL, PROLONGED QRS COMPLEX (WOLFF, PARKINSON, WHITE SYNDROME). REPORT OF FOURTEEN CASES AND A REVIEW OF THE LITERATURE \*

By ISIDORE STEIN, Captain, M.C., A.U.S., *Fort Ord, California*

IN 1930 Wolff, White and Parkinson<sup>1</sup> described a series of cases which showed an electrocardiographic picture of bundle branch block and a short P-R interval. This syndrome has since come to bear their names. It is characterized by attacks of paroxysmal tachycardia and carries only the danger attendant upon this phenomenon. The interim tracing shows a short P-R interval and prolonged QRS complex. It is considered essentially benign and these authors attribute these findings to vagal action. If this is removed by means of exercise or atropinization, the electrocardiogram is restored to normal.

Wolferth and Wood<sup>2</sup> and Holzmänn and Scherf<sup>3</sup> independently suggested that an accessory pathway existed between the auricles and ventricles which short-circuited the impulse from the sinus node to the ventricular musculature without having it pass through the A-V node and bundle. This pathway corresponds to the one described by Kent<sup>4</sup> in 1914. Further evidence in support of this hypothesis was advanced by the experimental work of Butterworth and Poindexter<sup>5</sup> who, working with dogs, established an artificial electrical pathway between the auricles and ventricles. Stimulation of this demonstrated the electrocardiographic picture of the short P-R interval, and prolonged QRS complex. Reversal of the flow from ventricle to auricle caused typical auricular tachycardia. Histologic proof of the existence of accessory conduction connections between the auricles and ventricles was recently demonstrated by Wood, Wolferth and Geckeler<sup>6</sup> on a patient who before death presented this electrocardiographic picture.

This report includes 14 cases of the Wolff, Parkinson, White syndrome seen over a period of 18 months at an Army Regional Hospital. Some of these patients were asymptomatic, others presented complaints which were not suggestive of organic heart disease.

## CASE REPORTS

*Case 1.* A 22 year old male who presented a history of attacks of tachycardia since 1940, six months prior to entry into the military service, had had about 20 attacks up until the time of first admission.

This soldier had been in the hospital on several occasions. The first time the electrocardiogram demonstrated a nodal paroxysmal tachycardia (rate 210 per min.) (figure 1c). Subsequent tracings taken during symptom-free periods showed biphasic

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From ASF Regional Hospital, Fort Ord, California.

T<sub>1, 2 and 3</sub>, short P-R interval (.06 sec.) and prolonged QRS (.16 sec.) (figure 1b). The next electrocardiogram taken several months later was normal (figure 1a). Another taken two days later showed the short P-R interval (.06 sec.) and prolonged QRS (.16 sec.) only in the first lead. After moderate exercise these abnormalities disappeared (figure 1d). Administration of atropine, quinidine and digitalis in full doses at different intervals failed, however, to affect the path of the impulse.

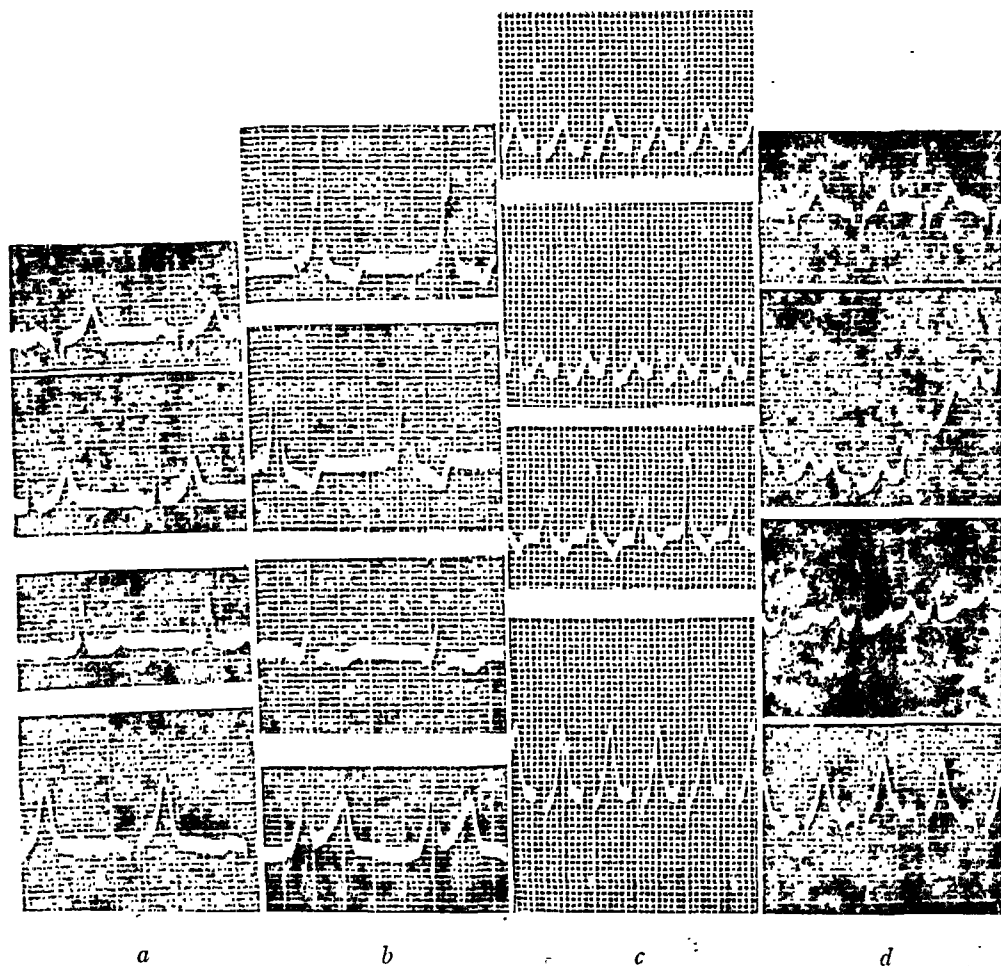


FIG. 1. Case 1. (a) Normal tracing. (b) P-R interval .06 sec.; QRS complex .16 sec.; T<sub>1, 2, 3</sub> inverted. (c) Period of tachycardia. Nodal rhythm. (d) Findings disappeared following exercise.

In this case the pathway of the impulse shifted from the A-V bundle to the so-called bundle of Kent at different and unpredictable times. Increasing the cardiac rate by means of exercise was sufficient in this instance to restore the normal pathway.

Case 2. This 19 year old male complained of abdominal cramps and headaches of two years' duration. Examination: Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. No abnormal cardiac signs were found. Sedimentation rate was normal.

Electrocardiographic studies revealed a left axis deviation, P-R interval of .10 sec. and QRS complex of .16 sec., inverted T<sub>1</sub> and biphasic T<sub>4</sub> (figure 2a). No change was noted on further tracings taken after exercise, atropinization, or full courses of quinidine and digitalis.

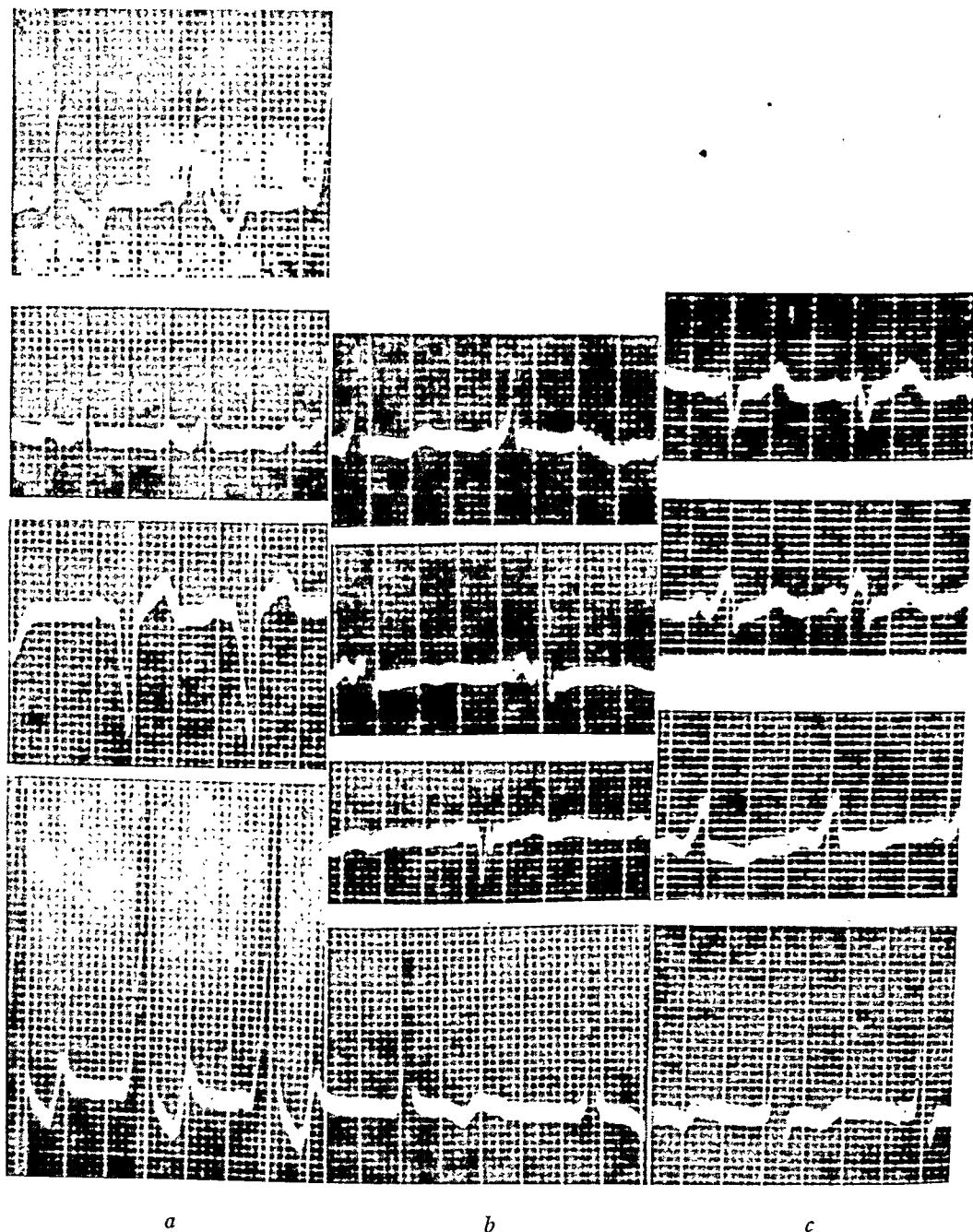


FIG. 2. *Case 2.* (a) P-R interval .10 sec.; QRS complex .16 sec.;  $T_1$  inverted,  $T_4$  biphasic. Left axis deviation. (b) *Case 3.* P-R interval .08 sec.; QRS complex .12 sec.;  $T_1$  biphasic,  $T_2$  low voltage,  $T_4$  biphasic. Left axis deviation. (c) *Case 4.* P-R interval .08 sec.; QRS complex .16 sec. Left axis deviation (except in first lead where these values are normal), right axis deviation.  $T_4$  biphasic.

*Case 3.* This 27 year old male presented no complaints whatever. Blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. There were no unusual cardiac findings. Electrocardiogram showed a short P-R interval (.08 sec.), a prolongation of the QRS complex (.12 sec.), left axis deviation, biphasic  $T_1$ , low voltage  $T_2$  and biphasic  $T_4$  (figure 2b).

*Case 4.* Seven years before admission, following numerous family reverses, this 38 year old male had an attack of "rapid heart beat." Since that time he had been very "nervous." On admission he claimed to be short of breath on moderate exercise. Examination: Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. There were no abnormal cardiac findings.

Electrocardiographic studies demonstrated a P-R interval of .08 sec. and a QRS interval of .16 sec. (except in the first lead where these values were normal), right axis deviation and a biphasic  $T_4$  (figure 2c). There was no appreciable change following a course of quinidine. Full digitalization produced a decrease in the QRS

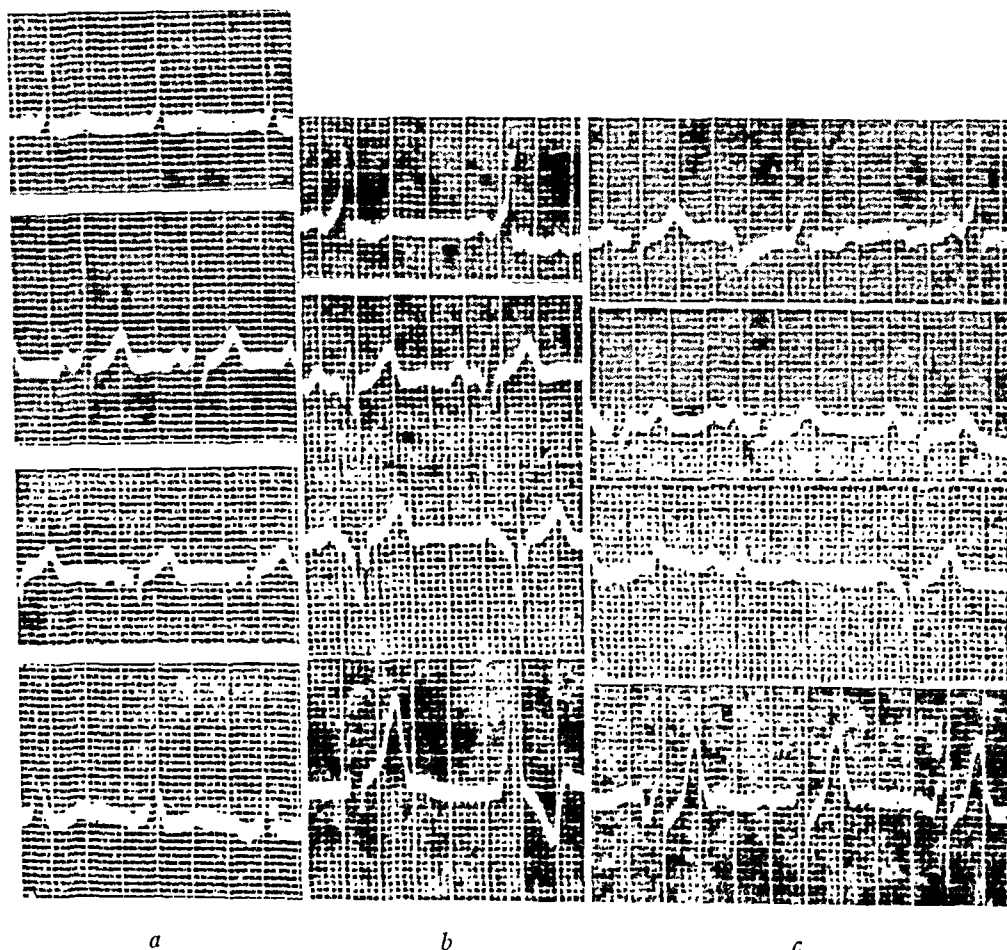


FIG. 3. (a) *Case 5.* P-R interval .08 sec.; QRS complex .12 sec. (b) *Case 6.* P-R interval .10 sec.; QRS complex .14 sec. Left axis deviation. Lead II is normal. In Lead IV three normal complexes are followed by a similar number of aberrant ones. (c) *Case 6.* Change of pathway of impulse (normal and aberrant) seen in Leads I and III.

interval in Lead I to .12 sec. and the expected depression and inversion of  $RT_4$ . The electrocardiogram was unaffected by exercise or the administration of full doses of atropine.

*Case 5.* On admission this 26 year old male had no complaints. Examination: Blood pressure was 140 mm. Hg systolic and 82 mm. diastolic. A short, soft systolic murmur was heard at the apex and pulmonic area. After exercise the latter murmur became harsh and was transmitted along the left border of the sternum. No thrills were felt.

Electrocardiographic investigation revealed a P-R interval of .08 sec. and a QRS of .12 sec. (figure 3a).

*Case 6.* This 24 year old male entered the hospital complaining of backaches and occasional sharp momentary left chest pain unrelated to exertion, over a period of years. No unusual cardiac signs were elicited. Routine laboratory studies were normal.

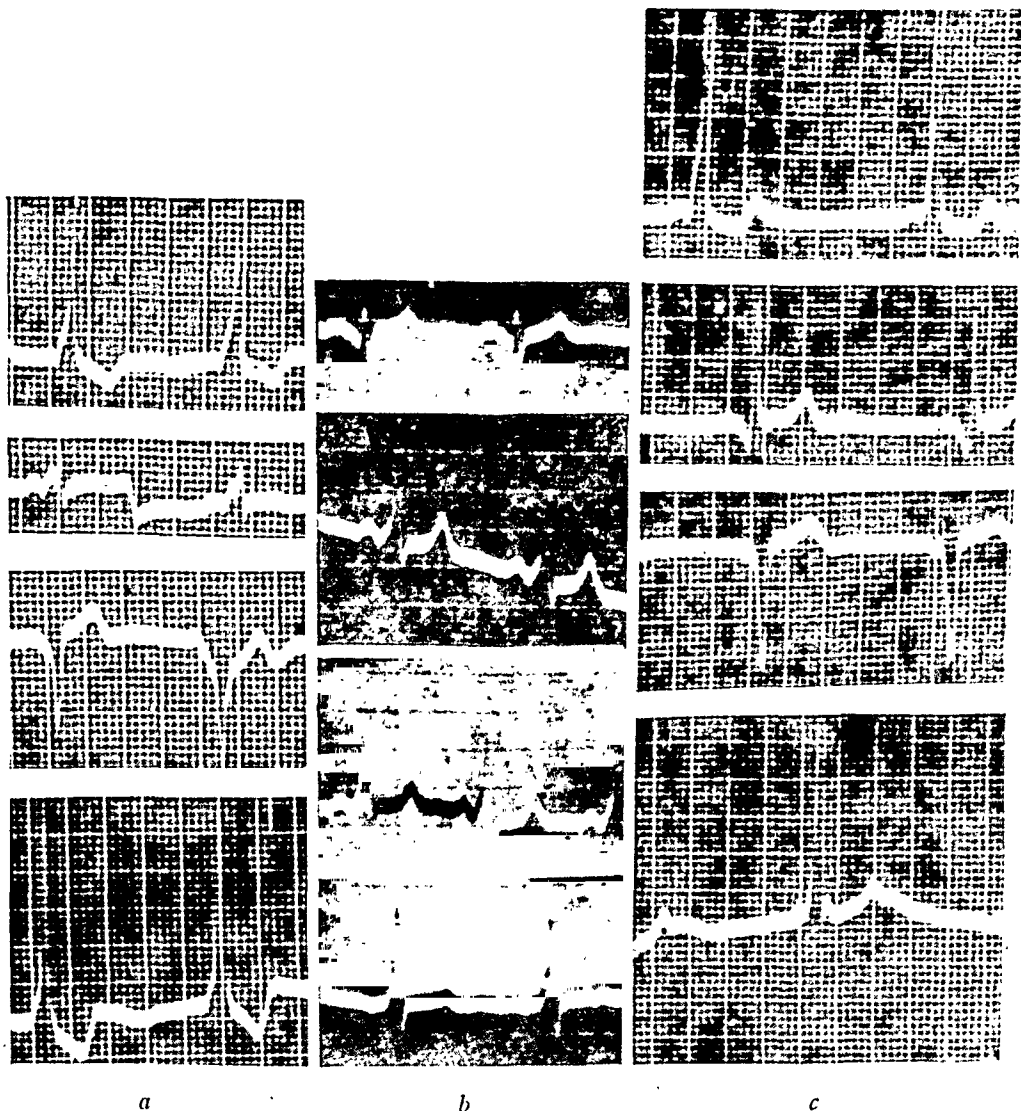


FIG. 4. (a) *Case 7.* P-R interval .08 sec.; QRS complex .12 sec.;  $T_1$  inverted,  $T_4$  biphasic. Left axis deviation. (b) *Case 8.* P-R interval .10 sec. and QRS complex .12 sec. in all but Lead I which is normal. These values are unaffected by exercise. (c) *Case 9.* P-R interval .08 sec.; QRS complex .13 sec.

The electrocardiogram showed a P-R interval of .10 sec. and QRS complex of .14 sec. and left axis deviation. The second lead was normal and in the fourth lead three normal complexes were followed by a similar number of aberrant ones (figure 3b). This patient showed a similar alternation in Leads I and III (figure 3c). At other times his tracings were practically normal. It is apparent that in this individual the path of the impulse from the sinus node was not a stable one.

*Case 7.* This 24 year old male complained of "smothering of his heart" at night which awakened him. This "smothering cut off his breath" and made him "hot and nervous." These symptoms have been present for two years before admission to the hospital. He denied ever having had rheumatic fever or hypertension. Examination: Blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. No unusual cardiac findings were discovered.

The electrocardiogram demonstrated a P-R interval of .08 sec., QRS complex of

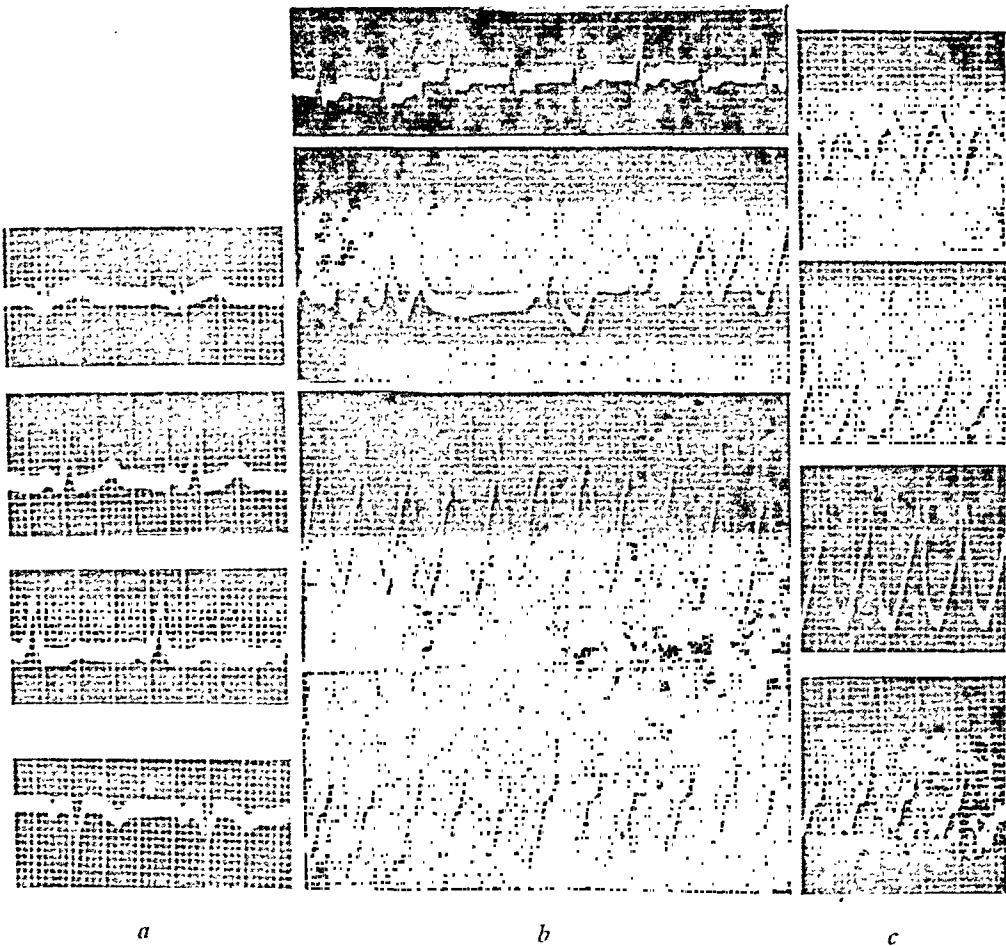


FIG. 5. (a) *Case 11.* P-R interval .10 sec.; QRS complex .12 sec.;  $T_1$  inverted. No change after exercise. Slight changes in  $T_4$  following atropinization. (b) *Case 11.* During an attack of tachycardia. Note that in Lead II there is a change from nodal tachycardia to several interval complexes (short P-R and prolonged QRS) and then the appearance of ventricular paroxysmal tachycardia. (c) *Case 11.* Same attack as seen in b. Ventricular paroxysmal tachycardia.

.12 sec., left axis deviation, inverted  $T_1$  and biphasic  $T_4$  (figure 4a). This picture was unaffected by exercise, atropine, and full doses of quinidine or digitalis.

*Case 8.* This 26 year old soldier stated he had had trouble with his "heart" since the age of 14 years. At that time he was confined to bed with polyarthritis and since has been unable to do strenuous activity because of pain and "fluttering" of his heart. He has also complained, during this period, of irregular pain and stiffness in his knees, ankles, and hip joints. On examination no abnormal physical signs were elicited.



Electrocardiographic studies revealed a P-R interval of .10 sec. and QRS complex of .12 sec. in all but the first lead. These features were unaffected by exercise (figure 4b).

*Case 9.* A young soldier on routine electrocardiographic studies revealed a left axis deviation, P-R interval of .08 sec. and a QRS complex of .13 sec. (figure 4c). Unfortunately this patient did not return so that his history and physical findings were unknown.

*Case 10.* A young soldier on routine electrocardiographic studies showed a P-R interval of .09 sec., QRS complex of .14 sec., depressed  $RT_{1 \text{ and } 4}$ , elevated  $ST_3$ , biphasic  $T_4$ , and left axis deviation. No essential change appeared following exercise.

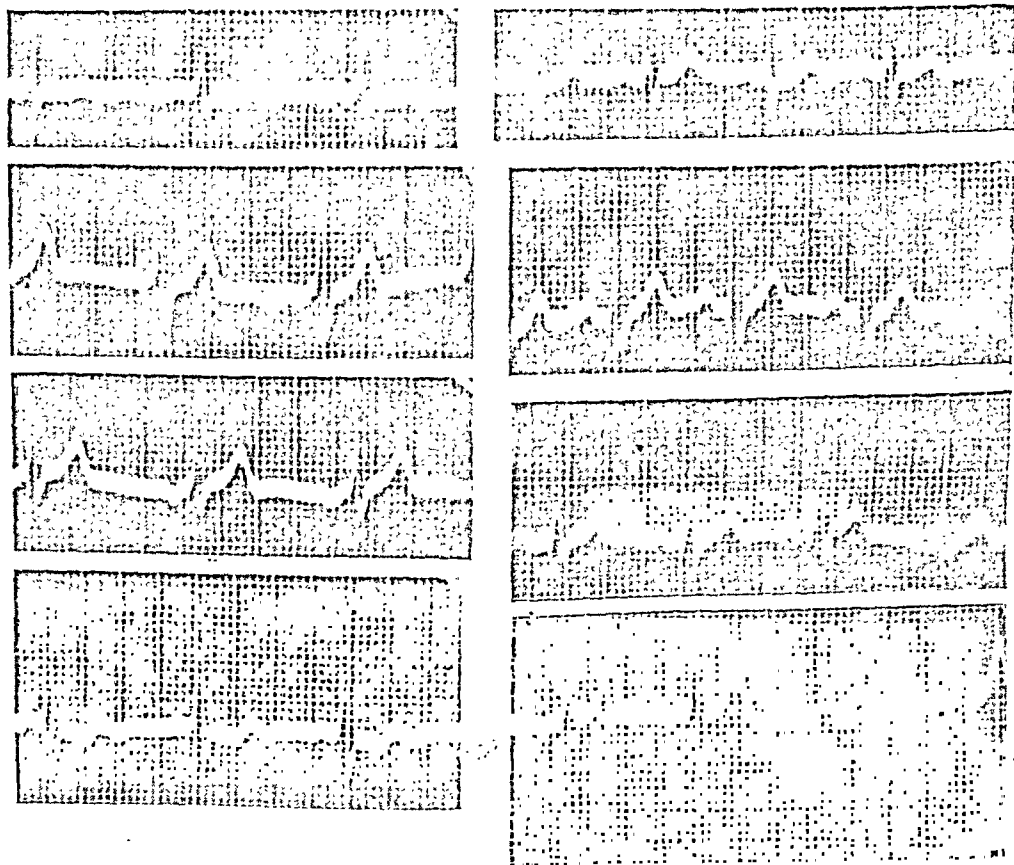


FIG. 6. *Case 12.* P-R interval .10 sec.; QRS complex .12 sec.;  $T_4$  biphasic. Tracing taken two hours later, normal.

This soldier left the post immediately after this tracing was taken which prevented further clinical investigation.

*Case 11.* This patient was a 36 year old female who told of attacks of "rapid heart beat" since the age of 13 years. During these periods which endured for a few minutes to a few hours, she became dizzy and weak. She did not present any other complaints. She felt well enough between spells to engage in occupations requiring strenuous physical activity.

She was examined on numerous occasions and at no time were signs of organic heart disease found. Roentgenograms of her chest revealed the heart shadow within normal limits. Sedimentation rate determinations were normal. During one of her

attacks, she showed a picture of nodal tachycardia (figure 5*a, b, c*) which changed to a ventricular focus within a short space of time. Interim electrocardiographic studies showed a PR interval of .10 sec. and a QRS complex of .12 sec. and an inverted  $T_4$ . The administration of full doses of atropine produced only slight changes in  $T_4$ . Following the intake of quinidine sulfate gr. v four times daily over a period of three weeks, the fourth lead became normal. The course of the impulse, however,

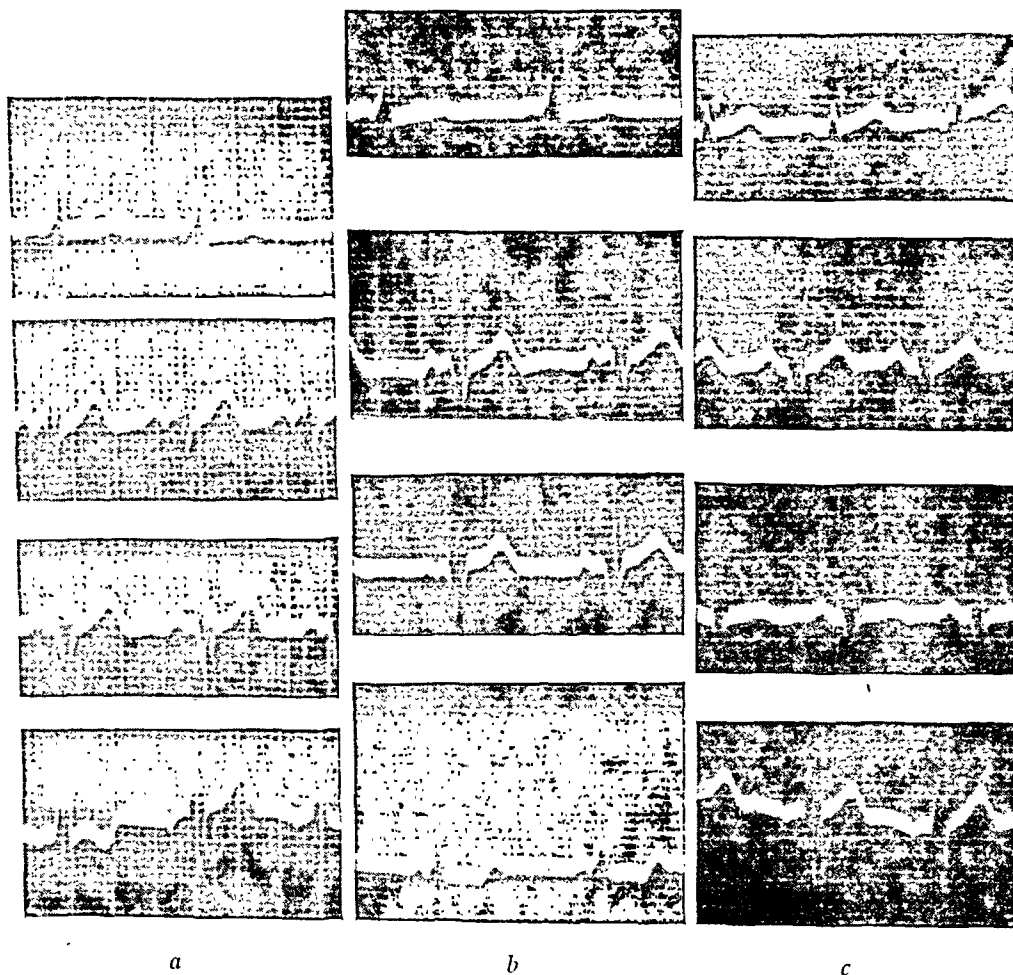


FIG. 7. (a) Case 13. P-R interval .08 sec.; QRS complex .12 sec. Note that in Lead III these intervals are normal. In Lead IV abnormal and aberrant beats alternate. The rhythm is unaffected by exercise. (b) Case 13. No essential change following atropinization. (c) Case 13. Normal tracing following quinidine sulfate (20 grains daily over a three week period).

in the other three leads was unaffected, as manifested by the unchanged PR interval (.08 sec.) and QRS complex (.16 sec.), and  $T_4$  was upright.

*Case 12.* This patient, a 25 year old male, presented a history of dizziness followed by "palpitation" when exercising or lifting heavy objects as well as while resting quietly in bed. The "palpitation" endured for 10 to 20 minutes and stopped suddenly with a "thump." Between attacks he felt well except for some moderate shortness of breath. Physical examination was essentially negative except for transient elevation of his blood pressure. Sedimentation rate was normal and no chamber enlargement was discovered during fluoroscopic examination of the heart.

The electrocardiographic picture consisted of a PR interval of .10 sec., QRS complex of .12 sec. and biphasic  $T_4$ . A tracing taken two hours later without any medication being given was normal in all respects (figure 6).

*Case 13.* This 18 year old soldier gave a history of having been struck by a car at six years of age. He was unconscious for two days. Since then he has had attacks of "rapid heart beat" on the average of about once a month, usually precipitated by sudden stooping or bending. Between attacks he felt perfectly well and demonstrated no symptoms of diminished cardiac reserve. During his stay in the hospital he contracted pneumonia from which he made an uneventful recovery. Examination of his heart did not reveal any abnormalities. Sedimentation rate and fluoroscopic studies were normal.

Electrocardiographic tracings revealed PR of .08 second and QRS of .12 second (figure 7a, b, c). These findings were absent in the third lead and in the fourth lead normal and aberrant beats alternated. This rhythm was unaffected by exercise or atropinization. Quinidine therapy, 20 grains daily for three weeks, produced a normal configuration of the electrocardiogram. When this medication was discontinued the abnormal pathway again became ascendant. Subsequent administration of quinidine reversed this to normal. Digitalization had no appreciable effect on this patient's electrocardiogram.

This individual did not present a stable picture. Adequate doses of quinidine brought a reversal to the normal electrocardiographic pattern.

*Case 14.* A 26 year old soldier gave a history of attacks of "rapid heart beat" for five years before admission in June 1945, appearing and disappearing suddenly and lasting anywhere from five minutes to five hours. These attacks bore no relation to exertion and patient felt that there was no one cause for these disturbances. He did notice, at times, that he had a lot of "gas" in his stomach and he belched a great deal when in the midst of an attack. During the tachycardia he became extremely "nervous." In between attacks he felt perfectly well although he occasionally noticed a "skip" in his heart. He did not have any symptoms of diminished cardiac reserve and there was no history of rheumatic fever, diphtheria, or hypertension.

When seen for the first time patient had a cardiac rate of between 180 and 200 beats per minute. Moderate pressure on the left carotid sinus promptly restored a slow regular rate of about 84 per minute. No electrocardiogram was taken at that time. There were no other unusual findings on physical examination. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic.

Electrocardiogram taken on the day after admission revealed a short PR and prolonged QRS interval. There was no essential change in the configuration of this tracing after exercise, full atropinization, adequate doses of quinidine, and digitalization.

A search for foci of infection in dental, urological, ear, nose, and throat systems proved futile. Roentgenograms of the chest and gastrointestinal tract were normal. Gastric analysis showed an achlorhydria (7 per cent alcohol). However, following histamine administration, free hydrochloric acid was within normal limits. Kahn reaction, blood count and urinalysis were all normal.

## DISCUSSION

Sufficient clinical and experimental data are now available for a rational explanation as to the course taken by the impulse in the heart of a patient with the Wolff, Parkinson, White syndrome. This pathway is not always the one of choice. In some individuals the sequence of events is a stable one; in others the aberrant bundle of Kent is employed irregularly. We can

see this in cases 1 and 6. On the other hand, in cases 2, 4 and 7 the short P-R interval and prolonged QRS complex appeared in the electrocardiogram consistently. In their original paper, Wolff, Parkinson, and White attributed the condition mainly to vagal influence, inasmuch as the release of vagal tone by exercise or atropinization produced a normal picture.

In Claggett's case <sup>7</sup> increasing the cardiac rate by means of exercise and atropine failed to produce a single normal complex.

*Effect of Atropine.* In this relation valuable information has been obtained through the use of various drugs. Diminishing the influence of the vagus by means of the administration of atropine should theoretically cause a return to normal rhythm. Claggett <sup>7</sup> was unsuccessful in his case in changing the electrocardiogram by atropine. We have produced the same effect (increasing the heart rate) through exercise, as noted in case 1, with resultant disappearance of the bundle-branch type of picture. On the other hand, we met with no success in the use of exercise or atropine in cases 2, 4, 7, 8, 11 and 13.

*Effect of Digitalis.* The effect of digitalis on this conduction disturbance has been tested. Theoretically, this drug should cause or perpetuate this picture. By depressing the A-V node, there would be encouragement for the use of the aberrant pathway.

Fox and Bobb <sup>8</sup> administered digitalis intravenously while the aberrant tissue was depressed and the conduction pattern normal, with resultant reappearance of the abnormal complex.

Similar findings were not obtained in our patients. Adequate digitalization did not affect the rhythm or conduction system in any of the patients who received this medication.

*Effect of Quinidine.* Because quinidine is considered to have greater affinity for the bundle of Kent, it is supposed to prevent this pathway from functioning in patients with a short P-R interval and a prolonged QRS complex. This would allow a normal course for the impulse through the A-V node and bundle, thus reestablishing the normal electrocardiographic pattern.

This was so in Fox and Bobb's case. <sup>8</sup> However, in the instances in which we employed this measure, we met with success in only one or possibly two cases. One patient (case 13) received quinidine sulfate in daily doses of 20 grains. After a period of three weeks his rhythm returned to normal. Cessation of the drug brought a reappearance of the abnormal conduction path. A subsequent trial of quinidine repeated the initial results. However, cases 1, 2, 4 and 7 continued with the abnormal pattern despite full doses of quinidine.

*Clinical Picture.* Aside from attacks of ectopic tachycardias these patients do not present any symptoms. <sup>9</sup> It is not felt that the complaints in case 2 (abdominal cramps and headaches), case 4 (nervousness and shortness of breath), case 6 (backaches and chest pain), case 7 ("smothering" spells and nervousness), and case 8 (joint pains) have any relationship

to the unusual electrocardiographic pattern. Fluttering of the heart in case 8 may have been due to attacks of an ectopic rhythm. All too often the condition is discovered as an incidental finding during a routine electrocardiographic examination.

*Prognosis.* The outlook in these individuals is in general encouraging. Their life expectancy is unaffected and their usefulness as citizens is unimpaired. They are prone only to the dangers attendant to paroxysmal tachycardia or circus rhythms. Should these be allowed to proceed unchecked for considerable lengths of time, the possibility of decompensation ensuing is present. Wood, Wolferth and Geckeler's<sup>6</sup> patient succumbed in what was probably an attack of an ectopic tachycardia.

*Treatment.* The only indications for treatment are for the periods of tachycardia. The therapy herein involved is too well known and does not fall within the scope of this paper.

### SUMMARY

1. Fourteen cases of Wolff, Parkinson, White syndrome are presented and a discussion of the literature undertaken.

2. The electrocardiographic findings are explained on the presence of an aberrant pathway between auricles and ventricles.

3. The expected results of the administration of such drugs as atropine and digitalis as described by some authors were not obtained with our patients. Quinidine sulfate depressed the abnormal pathway in only one, possibly two, of our cases. The remaining cases were unaffected.

### SUMMARY OF CASES

Cases	Stable	Exercise	Atropine	Digitalis	Quinidine
1	No	+	—	—	—
2	Yes	—	—	—	—
3	Yes (?)	—	—	—	—
4	Yes	—	—	—	—
5	Yes (?)	—	—	—	—
6	No	—	—	—	—
7	Yes	—	—	—	—
8	No (?)	—	—	—	—
9	Yes (?)	—	—	—	—
10	Yes (?)	—	—	—	—
11	Yes (?)	—	—	—	+ (?) in 4th lead
12	No	—	—	—	+
13	No	—	—	—	—
14	Yes	—	—	—	—

+ Effective in restoring normal rhythm.

— No effect on ECG.

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# LIVER FUNCTION STUDIES IN DIABETES MELLITUS \*

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THE liver is intimately associated with the storage of glycogen, the maintenance of the normal blood sugar level and the formation of ketone bodies. The important rôle of the liver in carbohydrate metabolism makes the investigation of liver function in diabetes mellitus pertinent. The present communication is concerned with the study of hepatic disease as determined by the serum colloidal gold reaction in 247 patients with diabetes mellitus.

Although hepatic enlargement has been noted in patients with diabetes mellitus by White,<sup>1</sup> Hanssen,<sup>2</sup> Joslin,<sup>3</sup> Warren,<sup>4</sup> and Marble,<sup>5</sup> there are few conclusive reports in the literature of liver function studies in this disease. Rabinowitch<sup>6</sup> reported positive van den Bergh reactions in 34 of 130 patients with diabetes. He noted abnormal urobilinogen excretion in the urine in only three of 50 patients. Diamond,<sup>7</sup> however, found normal van den Bergh reactions in 14 of 17 diabetic patients. Meyer<sup>8</sup> observed hepatic dysfunction as determined by the quantitative van den Bergh reaction and urobilinogen excretion studies in 28 of 100 patients with diabetes mellitus. Hanssen<sup>2</sup> found a normal icteric index and urobilinogen excretion in diabetic patients with hepatic enlargement. Marble<sup>5</sup> also reported normal plasma bilirubin determinations in eight patients and normal cholesterol/cholesterol-ester ratios in 29 of 30 patients with diabetes mellitus.

## METHODS

The serum colloidal gold reaction was selected for this study because of its marked sensitivity in detecting early liver disease. The reaction was found positive by one of us<sup>9</sup> in 92 per cent of patients with hepatic disease, false positive reactions occurring rarely in the control groups. The sensitivity and reliability of the colloidal gold reaction has been confirmed by Loew and Noth<sup>10</sup> and by Mateer and co-workers.<sup>11</sup> Sweet, Gray and Allen<sup>12</sup> found the test most sensitive in detecting liver disease in hepatolenticular degeneration, and Batty and Gray<sup>13</sup> utilized the reaction in investigating liver involvement in gall-bladder disease. Andersch<sup>14</sup> found the colloidal gold reaction exceedingly sensitive in evaluating the hepatic damage associated with sulfonamide therapy, and MacLagen<sup>15</sup> found "the test a valuable indicator of liver damage." Lavin, Sellek and del Frade<sup>16</sup> concluded from their studies that the serum colloidal gold test was "one of the most sensitive liver function tests." Similar results were obtained by Gidekel<sup>17</sup> and

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Forns<sup>18</sup> who reported the reaction to have "great sensitivity as an index of liver disease" and who recommended its routine use in the diagnosis of hepatic disease.

The serum colloidal gold reaction is based upon the fact that colloidal gold is precipitated by the diluted serum from a patient with hepatic disease but not by normal serum.<sup>9</sup> The mechanism of the reaction depends upon an increase in the gamma globulin and a decrease in the albumin content of the serum of patients with liver disease.<sup>10</sup> Five c.c. of acidified colloidal gold are added to 1 c.c. of serum diluted to 1:3,500, 1:7,000, and 1:14,000 as described in previous reports.<sup>13</sup> The degree of flocculation is recorded as in the Lange reaction. A positive reaction is represented by complete flocculation in one or more dilutions.

The 247 patients with diabetes were divided into two groups. Group A consisted of 99 patients who had been under careful supervision for the management of their diabetes in a private institution for several years. Their diet, insulin requirement and general care were subject to fairly careful control. Group B was composed of 148 patients receiving treatment for diabetes in a charity institution. The economic, social and intellectual status of this group made dietary control and insulin treatment more difficult. Clinic visits were less frequent in Group B than in Group A, and the general care of these patients regarding infections, vitamin intake and control of the blood sugar levels was not equal to that of Group A.

The incidence of liver disease in the obese and non-obese patients was studied in both groups. An increase in weight of more than 10 per cent over the standard weight was considered evidence of obesity. Observations in the age groups of patients under 35 and over 35 years of age were also made.

The frequency of positive liver tests in mild and severe diabetes was investigated. The 247 patients were divided arbitrarily into two groups. Those requiring less than 25 units of insulin daily were placed in the classification of mild diabetes, and the others requiring 25 or more units of insulin daily were defined as severe diabetics.

The relationship of liver involvement to the proper control of the diabetes was investigated. The factors noted in evaluating the control of the diabetes were the level of hyperglycemia, glycosuria, acidosis, hypoglycemia, infections and other complications, insulin resistance and rapid fluctuations in insulin requirement. The incidence of positive liver tests in patients with acidosis or coma was studied also.

## RESULTS

The serum colloidal gold reaction was positive in 91 of the 247 patients with diabetes, an incidence of 36.8 per cent (table 1). Positive reactions occurred more frequently in the 148 patients of Group B (43.2 per cent) than in the 99 patients of Group A (27.1 per cent).



TABLE I  
Incidence of Liver Disease in Diabetes

	Number of Patients	Positive Serum Colloidal Gold Reactions
Group A	99	27 (27.1%)
Group B	148	64 (43.2%)
Total	247	91 (36.8%)

The test was positive in 28 of the 66 obese patients (42.4 per cent) as compared with 63 of the 181 patients (34.8 per cent) in the non-obese group (table 2). In Group B the incidence appeared to be higher in both the obese (59.2 per cent) and non-obese patients (39.6 per cent) than in the corresponding patients of Group A in which positive results were observed in 30 per cent and 25 per cent respectively.

TABLE II  
Incidence of Liver Disease in Obese and Non-Obese Diabetic Patients

	Obese Patients	Positive Liver Tests	Non-Obese Patients	Positive Liver Tests
Group A	39	12 (30%)	60	15 (25%)
Group B	27	16 (59.2%)	121	48 (39.6%)
Total	66	28 (42.4%)	181	63 (34.8%)

There appeared very little difference between the incidence of liver involvement in patients under 35 years of age (43.4 per cent) and that in the older age group (34.8 per cent). Here again the percentage was higher in Group B (48.4 per cent and 41.7 per cent) than in Group A (30.7 per cent and 25.5 per cent) (table 3).

Hepatic disease appeared to be much more prevalent in severe diabetes than in mild diabetes. The colloidal gold reaction was positive in 62 of 123

TABLE III  
The Relation of Age to Positive Liver Tests in Diabetic Patients

	Number of Patients	Positive Serum Colloidal Gold Reactions
<i>Under 35</i>		
Group A	13	4 (30.7%)
Group B	33	16 (48.4%)
Total	46	20 (43.4%)
<i>Over 35</i>		
Group A	86	22 (25.5%)
Group B	115	48 (41.7%)
Total	201	70 (34.8%)

patients with severe diabetes (49.9 per cent) compared with 29 of 124 patients with mild diabetes (23.3 per cent) (table 4). Positive tests were observed with almost equal frequency among the patients of Group A and Group B, with severe diabetes, occurring in 47.2 per cent of the former and 52.3 per cent of the latter. Among the mildly diabetic patients, however, the incidence was higher in Group B (30.6 per cent) than in Group A (16.1 per cent).

TABLE IV  
Incidence of Positive Liver Tests in Mild and Severe Diabetes

	Number of Patients	Incidence of Positive Colloidal Gold Reaction
<i>Mild Diabetes</i>		
Group A	62	10 (16.1%)
Group B	62	19 (30.6%)
Total	124	29 (23.3%)
<i>Severe Diabetes</i>		
Group A	37	17 (47.2%)
Group B	86	45 (52.3%)
Total	123	62 (49.9%)

The highest incidence of liver involvement occurred in the poorly controlled diabetic patients (table 5). The colloidal gold test was positive in 48 of 84 patients (57.1 per cent) with essentially the same incidence in Group A (54 per cent) and Group B (58.6 per cent). This is to be contrasted with the occurrence of hepatic disease in only 43 of 163 patients

TABLE V  
Positive Liver Tests in Well Controlled and Poorly Controlled Diabetes

	Number of Patients	Incidence of Positive Colloidal Gold Reaction
<i>Well Controlled</i>		
Group A	73	13 (17.7%)
Group B	90	30 (33.3%)
Total	163	43 (26.3%)
<i>Poorly Controlled</i>		
Group A	26	14 (54%)
Group B	58	34 (58.6%)
Total	84	48 (57.1%)

(26.3 per cent) with well controlled diabetes (table 5). Among these patients positive tests were more prevalent in Group B (33.3 per cent) than in Group A (17.7 per cent).

Twenty-two patients were in diabetic coma or acidosis when their liver function was studied. In 17 of these, or 77.2 per cent, positive colloidal gold reactions were observed (table 6).

TABLE VI  
Incidence of Hepatic Disease in Diabetic Acidosis and Coma

Number of Patients	Positive Serum Colloidal Gold Reactions
22	17 (77.2%)

## DISCUSSION

It has been known for a long time that the diabetic patient is susceptible to fatty infiltration of the liver<sup>1, 2</sup> and to depletion of the liver glycogen.<sup>3, 4</sup> It was not surprising, therefore, to find evidence of liver involvement in 36.8 per cent of the 247 diabetic patients studied. This incidence of hepatic disease was somewhat higher than that reported by Meyer<sup>8</sup> and Rabino-witch.<sup>6</sup>

Newburgh and his associates have described a syndrome of hyperglycemia, glycosuria and a decreased glucose tolerance occurring in obese individuals and resulting presumably from fatty infiltration of the liver.<sup>20</sup> A higher incidence of liver involvement in obese than in non-obese patients could be anticipated from his studies. However, there was no significant statistical difference in the incidence of positive colloidal gold reactions in the 66 obese and 181 non-obese diabetic patients reported in this section (table 2). This may be explained by Newburgh's observation that the "glucose tolerance is unimpaired until the obesity has existed for more than 11 years."<sup>20a</sup> Since many of the patients reported in table 2 had not been obese for more than five or six years, not enough time had elapsed, apparently, to produce a fatty infiltration of the liver.

Although diabetes is usually more severe in the young than in the aged, there was no significant statistical difference in the incidence of hepatic involvement in the two groups (table 3). The greater regenerative powers of the liver in the young<sup>4</sup> and the shorter duration of the disease may have compensated for the increased severity of the diabetes.

There was a most striking difference in the incidence of positive colloidal gold reactions in the 124 patients with mild diabetes when compared with the 123 patients with severe diabetes. The liver test was positive in 23.3 per cent of the mild diabetics and in 49.9 per cent of the severe diabetics, an increase of over 100 per cent (table 4).

The high incidence of positive liver tests in severe diabetes is presumably the result of fatty infiltration of the liver which is a common occurrence in this disease. The extreme degree of fatty infiltration of the liver occurring in depancreatized dogs is well known,<sup>21</sup> and it is probable that the hepatomegaly commonly observed in juvenile and adult diabetics represents fatty infiltration of the liver in most instances.

Failure to control the diabetic state properly results in a considerable increase in the incidence of liver disease. The effects of poor diabetic control on the liver have been observed by White<sup>1</sup> who reported the common occurrence of fatty infiltration of the liver in poorly treated diabetic children. The liver decreased in size after the administration of insulin and the institution of diabetic management. Failure to control the diabetes in experimental animals, moreover, has resulted in marked fatty infiltration of the liver.<sup>22</sup>

The frequency of hepatic involvement in the 247 diabetic patients under discussion was increased from 26.3 per cent in the well controlled diabetics to 57.1 per cent in the poorly controlled group (table 5). This represents an increase of more than 100 per cent in the latter group and emphasizes the importance of the proper regulation of this disease.

In reviewing tables 1 to 3 it was observed that the patients in Group B consistently demonstrated a higher incidence of liver involvement than those in Group A. Positive tests were noted in 16.1 to 29.2 per cent more patients in Group B. The determining factors in this discrepancy between the two

groups were the lapses of insulin therapy and the lack of general care in regard to the diet and infections. Since the patients in this group were at a lower intellectual and economic level than those in Group A, differences in dietary habits and the intelligent use of insulin were important considerations. This was confirmed by the fact that in the poorly controlled diabetics (table 5) and in the severe diabetics (table 4) the incidence of positive liver tests was essentially the same in both groups.

An exceedingly high incidence of hepatic disease was observed in 22 patients with acidosis or coma. Positive colloidal gold reactions occurred in 17 instances, or 77.2 per cent (table 6). In liver disease there appears to be a disturbance in the functional capacity of the liver cells to deposit glycogen. This can be demonstrated by the use of hepatotoxic agents and has been observed in association with diseases of the liver.<sup>23</sup> When the liver reserves of glycogen are depleted, ketonemia is more likely to occur.<sup>24</sup> There is a definite relationship between hepatic disease, glycogen reserve and ketosis.<sup>25</sup> The importance of a high carbohydrate diet in this group is quite evident.

These studies of the colloidal gold reaction in diabetes support the views of Soskin<sup>26</sup> and others that there is a close relationship between hepatic disease and diabetes. It is generally recognized that the glycogen stores of the liver have an important bearing upon its functional capacity and upon its resistance to hepatotoxic agents. In diabetes the glycogen stores of the liver are frequently depleted and are replaced by fat, particularly in the severe manifestations of the disease. The high incidence of positive colloidal gold reactions in these cases emphasizes the importance of the liver disease in severe diabetes.

The liver, moreover, is the principal organ for the homeostatic regulation of the blood sugar level. Soskin and his associates have noted that whenever the blood sugar tends to rise above the normal level, the liver responds by diminishing its output of sugar into the blood. Insulin is an important factor in the endocrine balance which controls the level at which the liver regulates the blood sugar, but the intrinsic homeostatic regulating mechanism of the liver is thought to be the most important factor of all.<sup>26</sup>

When the liver is abnormal, the mechanism by which it regulates the blood sugar is greatly impaired, and its response to insulin is diminished. The detection of liver disease in approximately 50 per cent of patients with severe diabetes may be of considerable significance in the dietary and medical management of the disease.

#### SUMMARY

1. The serum colloidal gold reaction was positive in 91 of 247 patients with diabetes, an incidence of 36.8 per cent. Liver involvement was observed more frequently in the 148 patients receiving irregular care (43.2 per cent) than in the 99 patients under constant supervision (27.1 per cent).

2. The reaction was positive in 62 of 123 patients with severe diabetes (49.9 per cent) in contrast to 29 of 124 patients (23.3 per cent) with mild diabetes.

3. The frequency of hepatic involvement was increased from 26.3 per cent in the well controlled diabetics to 57.1 per cent in the poorly controlled group.

4. The highest incidence of hepatic disease was found in 22 patients with diabetic acidosis or coma. The test was positive in 17 instances (77.2 per cent) in this group.

5. Positive reactions were observed in 28 of 66 obese patients (42.4 per cent) as compared with 63 of the 181 non-obese patients (34.8 per cent).

6. The incidence of liver involvement was 43.4 per cent in the patients under 35 years of age and 34.8 per cent in the older age group.

### CONCLUSIONS

1. Diabetes mellitus is associated frequently with disease of the liver as is evidenced by the presence of a positive serum colloidal gold reaction.

2. Hepatic involvement is much more prevalent in severe than in mild diabetes.

3. Failure to control the diabetic state properly results in a considerable increase in liver disease as is seen particularly in patients with acidosis or coma.

4. There is no statistically significant difference between the frequency of liver involvement in the younger and older age groups and that in obese and non-obese patients.

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# WHAT CAN BE ACCOMPLISHED IN THE TREATMENT OF HEART DISEASES \*

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It is not out of place now and then to take stock of what we can expect at the time as the maximum hope in the treatment of diseases of the heart. Especially is this an encouraging process when we bring into focus the tremendous advances that have been made in this field in the last quarter of a century. Diseases which were long thought to be beyond relief are now being treated by surgical and medical means with the appearance of cure.

*Congenital Heart Disease.* It is fitting that I should mention congenital heart disease first. Until recently nothing corrective could be done in the treatment of patients suffering from these defects. However, a new field was explored and opened when Gross <sup>1, 2, 3</sup> daringly conceived and executed the operation of ligation of a patent ductus arteriosus and apparently restored the circulation to a normal status. In this defect there is flow of blood from aorta to pulmonary artery by way of a patent ductus arteriosus. Ample cases have been subjected to this procedure to indicate that it can be carried out by competent surgeons with a minimum of mortality. When left to their natural course the outlook for these patients is usually one of heart failure or of bacterial endocarditis.<sup>4</sup> The operation appears indicated in those patients showing evidence of decreased circulation, namely underdevelopment and undernutrition<sup>5</sup> or evidence of subacute bacterial endocarditis.<sup>6</sup> Since this congenital defect is now subject to surgical cure, it is important that these cases be recognized and given the benefit of consideration for operation. The essential features contributing to the diagnosis are: continuous machinery murmur over the pulmonic area, pulmonary conus enlargement, thrill over the pulmonic area, wide pulse pressure, absence of axis deviation in electrocardiogram, left ventricular enlargement in roentgenogram, increased pulsation of the pulmonary artery, pulmonary vessels and left ventricular margin, absence of cyanosis, and stunted growth. It occurs in females twice as often as in males. Only those patients with uncomplicated patency of the ductus arteriosus should be subjected to operation. Only recently, Blalock and Taussig<sup>7</sup> have reported an operation for increasing the flow of blood through the lungs with the intention of reducing the cyanosis in patients with congenital malformations of the heart with pulmonary stenosis or atresia. The operation consists in making an anastomosis between a branch of the aorta and one of the pulmonary arteries. An artificial patent ductus arteriosus is created.

Although it is important and satisfying to arrive at a correct diagnosis,

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many of the congenital cardiac defects are multiple and present such complicated physical signs that accurate diagnosis is not always possible at present. One should recognize coarctation of the aorta in order to separate subjects exhibiting this from other patients with hypertension, both with respect to the natural history and complications, and also to spare such patients splanchnic resection for lowering the blood pressure. Moreover, the surgical approach to the rectification of the defect prevailing in coarctation of the aorta has been made recently by Gross and Hufnagel<sup>8a</sup> by resection of the zone of constriction with end to end anastomosis of the proximal and distal ends of the aorta. The presence of hypertension in the upper extremities, with lower or absent blood pressure and pulses in the femoral, popliteal, dorsalis pedis and posterior tibial vessels, enlargement of the heart to the left, a systolic murmur over the base of the heart, and scalloping of the lower margins of the ribs by erosion caused by the intercostal arteries, make up the clinical picture of coarctation of the aorta.<sup>8, 9</sup> It is urgent, therefore, in every patient exhibiting hypertension to measure the blood pressure in the legs as well as in the arms.

In my opinion insufficient information can be secured by diodrast visualization to warrant the dangers inherent in its injection.<sup>10</sup>

*Chronic Constrictive Pericarditis.* Chronic constrictive pericarditis or Pick's disease is another disease which can be cured in suitable cases by surgical intervention. Churchill, in Boston, first stimulated interest in pericardiectomy in this country.<sup>11</sup> He demonstrated that the operation could be safely carried out, and cured certain patients. Heuer, at the New York Hospital, has operated on 18 patients whom I have observed.<sup>12, 13, 14</sup> Beck,<sup>15</sup> Blalock<sup>16</sup> and Harrington<sup>17</sup> have also had a wide experience in this field. It is imperative that physicians recognize these cases and separate them from other cases of heart failure. In any patient who presents a picture of heart failure but in whom the usual common etiological causes are not found, that is, who show no evidence of rheumatic valvular disease, arteriosclerosis or hypertension, the diagnosis of chronic constrictive pericarditis should be considered.<sup>13</sup> There are venous engorgement, enlargement of the liver, ascites, edema, pleural effusion, small or not greatly enlarged heart, small pulse pressure, paradoxical pulse, small or absent pulsations of the heart under fluoroscopy and in roentgenkymograms, fixation of the heart in the chest on fluoroscopy and of the electrical axis of the electrocardiogram and low amplitude of the QRS complexes of the electrocardiogram. Calcification may be found on fluoroscopy and in the roentgenograms.<sup>18</sup> The signs and symptoms are due to the thickened pericardium obstructing the passage of blood through the heart: the heart is unable to relax in diastole to admit blood to its cavities, and is unable to contract completely in systole to expel blood from its cavities.<sup>19</sup> The venous pressure is elevated, the circulation time is prolonged, and the cardiac output per beat and per minute decreased. Dissecting off the parietal and visceral pericardium from as much of the anterior surface of the heart as possible, enabling it to herniate out through



this window, so improves the function of the heart that the circulation returns to normal limits and the patient improves and is restored to normal health and activity.<sup>14</sup>

We have followed patients from the stage of acute pericarditis with effusion through absorption of the fluid and then constriction by the thickening pericardium. Patients are leading normal lives after operation, as compared with invalidism beforehand. Improvement may be rapid, a matter of weeks, or it may take months or upward of a year for maximum benefit to be accomplished.<sup>14</sup> The care of these patients illustrates the benefits which accrue from the close collaboration of physician and surgeon.

*Carotid Sinus Syndrome.* This syndrome is characterized by hypersensitivity of one or both of the carotid sinuses. The bulbous enlargement at the bifurcation of the carotid artery into its external and internal branches is supplied with a plexus of nerve fibers through which impulses are mediated which aid in the maintenance of blood pressure. Pressure on the carotid sinus induces slowing of the heart and moderate fall in blood pressure. In marked hypersensitivity of the carotid sinuses, pressure on the sinus results in marked cardiac slowing even to asystole, fall in blood pressure to zero, and syncope.<sup>20</sup> Lesser grades of sensitivity result in slowing of heart rate, fall in blood pressure and dizziness. One or both sinuses may be hypersensitive. This *vagus* type is the most common. This type of reaction is abolished by atropine and by novocainization of the sinus. There is also a *depressor* type in which syncope results from cerebral anoxia due to fall in systemic blood pressure and a *cerebral* type in which syncope occurs without change in heart rate or blood pressure.<sup>20</sup> In those patients with hypersensitivity of the carotid sinus, attacks of syncope may be precipitated by turning the head, wearing a tight collar, leaning forward while reading a paper in a club type chair, or pressure on the sinus in resting the head on one hand. In carrying out tests for hypersensitivity, patients should be recumbent, and pressure applied first on one side, then on the other, and then bilaterally. Atropine should be ready in a syringe to inject at once if the response is prolonged. Auscultation over the heart and blood pressure should be taken during pressure, and if possible electrocardiograms should be done to record the prevailing rhythm.<sup>21</sup> If hypersensitivity is elicited, the effect of atropine should be observed, and on a later day, the effect of novocainization. If these abolish the reaction, if the sensitivity is marked, and if the spontaneous attacks are frequent and unforeseen, surgical intervention is indicated. Dr. Ray and I have been especially interested in this syndrome.<sup>21</sup> Earlier relief was afforded these patients by denervation of the sinus.<sup>21</sup> Recently Dr. Ray has devised an operation for its cure by the intracranial section of the ninth nerve on the affected side.<sup>22</sup> This syndrome is seen commonly in older individuals with arteriosclerotic changes in the vessels.

*Arteriovenous Aneurysms.* Arteriovenous aneurysms result from trauma, stabbings, or bullet wounds. The diagnostic signs of arteriovenous com-

munications are well known: thrills and bruits over the communication, increase in size of the contiguous vessels, and increase in the size of the part. The heart rate increases; the diastolic blood pressure is low and there is a wide pulse pressure; the circulating blood volume, the volume output of the heart and the heart size, all increase; the circulation time becomes shorter and the venous pressure in the part is elevated.<sup>23</sup>

With surgical closure and elimination of the communication all of these return toward or to their normal levels. Porter has found that an extreme degree of reducible cardiac dilatation can exist over a prolonged period with occurrence of only a minimal amount of cardiac hypertrophy and without the development of heart failure.<sup>23</sup>

*Aneurysm of the Aorta.* The surgical treatment of aneurysms has fascinated surgeons. Aneurysms in certain locations are amenable to ligation. The treatment of aneurysms of the aorta has, however, challenged surgical acumen. In recent years Blakemore and King<sup>24</sup> have reported success in the treatment of aneurysms by the following means: a fine insulated coin-silver wire is introduced through a needle into the aneurysm and passed on and on in and allowed to coil up in the aneurysmal sac. A direct electric current is then passed through the coils in order to encourage coagulation of the blood enmeshed in the coils. In the course of time the whole mass is replaced by fibrous scar tissue.

Recently Alexander and Byron<sup>25</sup> reported the ligation on both sides of and removal of an aneurysm which had developed above the constriction in coarctation of the aorta. In this case collateral channels with reversal of blood flow were already prepared by the congenital defect.

Recently Beck<sup>26</sup> has reported an attempted strengthening of an aneurysm of the left ventricle by the plastering over it and suturing to the edge of the opening made in the pericardium a patch of fascia lata large enough to cover the aneurysm.

*Hypertension.* The treatment of essential hypertension by medical means has not been spectacular or satisfactory. Much can be accomplished symptomatically by helping the individuals to adapt themselves to their problems and life situations, by inculcating the habit of relaxation, and by the moderate use of luminal. However, the course of the disease is rarely interrupted from following its usual patterns with cardiac, renal or cerebral involvement.<sup>27</sup> There has been tremendous interest in hypertension in recent years, and many investigations contributing to an understanding of hypertension have been made. But the fact still remains that the cause of hypertension is not known. Smithwick and others studied sections of the kidney removed at operation and found that no changes were apparent which placed the pathology at this stage in recognizable, anatomical changes in this organ.<sup>28</sup> The most interesting approaches to treatment have been the surgical ones which aim at the interruption of sympathetic nerve pathways. Without tracing the history of these operations it may be stated that the Smithwick procedure is the one which appears to accomplish most in lowering the blood

pressure.<sup>29</sup> The operation is done in two stages. The sympathetic communications are severed first on one side and 10 days to two weeks later on the other side as follows: thoracic 9 to lumbar 2 or 3 inclusive and the greater, lesser and least splanchnic nerves are sectioned.

In a recent lecture at the New York Academy of Medicine before the New York Heart Association, Smithwick reported lowering of blood pressure to normal levels in a large proportion of cases which were subjected to this treatment, and moderate lowering in many others.<sup>30</sup> Further investigation should help in selection of cases which might be expected to respond. Dr. Bronson Ray at the New York Hospital has found significant lowering of blood pressure in a sufficient number of patients from the Smithwick operation to pursue this operative procedure.<sup>30</sup> I have made observations on certain of these patients.<sup>31</sup>

Mention may be made, briefly, of the hypertension associated with pheochromocytoma (adrenal medullary tumor). Fall in blood pressure to normal, decrease in size of the heart, disappearance of the paroxysmal rises in blood pressure with sweating, decrease in basal metabolic rate, and regression of the changes in the eye grounds follow the successful location and removal of a tumor of the medullary portion of an adrenal gland.<sup>32</sup> Exploration of the opposite side should be carried out first before operation, to be certain that the adrenal is normal on that side. It is needless to say that exploration of the adrenals should be made before splanchnic resection for hypertension is carried out.

The status of unilateral nephrectomy for the relief of hypertension which may be associated with disease of one kidney remains to the future.

I have not been convinced of the value of thiocyanate in the lowering of blood pressure.<sup>33</sup> The dangers inherent in its use, namely mental alterations, lethargy, skin eruptions, weakness, nausea and vomiting, induction of goiter, all limit its application. Blood levels should be followed while the drug is being administered.

So-called depressor extracts, garlic and mistletoe, have no place in the treatment of hypertension.

*Angina Pectoris.* The onset of angina pectoris has been viewed gravely by the physician and with great fear by the patient. The reasons for this are several: (1) the grave implication about the state of the coronary vessels and inference from the life histories of other patients, and (2) the great fear of impending death with which the pain may be associated. Patients when free of pain are faced with its recurrence. Much can be accomplished in the care of these patients in reeducation about their activities, slowing down their speed of doing things, care about exertions in cold weather and after meals; nitroglycerine may be used for the acute episodes; aminophyllin 0.1 gm. t.i.d., theobromine and sodium acetate, enteric coated, 0.5 gm. q.i.d., or other vasodilators such as whiskey may be given in the attempt to induce more prolonged and continuous vasodilation. The side effects of nitroglycerine (throbbing and pounding of the heart) may be so disagreeable that some

patients refuse to use it. The frequent use of small doses may eliminate this objection. The use of testosterone and nicotinic acid does not appear to have any place in the treatment of angina. Quinidine 0.2 to 0.3 gm. q.i.d. may be effective<sup>34</sup>; I do not like to give this drug daily, however, over long periods of time. Recently, Freedberg and Riseman<sup>34a</sup> have observed benefit from the use of cobra venom. In many patients these measures are inadequate and other means have been sought. One of the most effective procedures is the interruption of the pain pathways in order to eliminate the pain. This can be done in two ways: the alcohol injection of the posterior root ganglia is one procedure. In some hands, namely White<sup>35</sup> in Boston, and Moore<sup>36</sup> at the Presbyterian Hospital in New York, it has found usefulness. The upper four thoracic ganglia may be injected (or T<sub>1</sub> to T<sub>5</sub> inclusive). Pleural effusion early and intercostal neuralgia later often make the cure more disagreeable than the disease. Horner's syndrome—enophthalmos, small pupil, drooping of lid and sweating may occur. In uncomplicated cases relief may be of months' and years' duration. If pain is bilateral, one side should be injected at a time.

The second method of interruption of pain sensation is to do posterior root section T<sub>1</sub> to T<sub>5</sub> on one side or bilaterally if indicated. This has found usefulness in the experience of White<sup>37</sup> and Ray.<sup>38</sup> In Ray's experience he would prefer this operation to alcohol injection and in the cases I have seen in whom Ray has carried out this procedure I have found it effective. On occasions they have recovered so rapidly as to be ambulatory in one week.

There are those who inquire about the wisdom of interrupting the pain signals. The relief which these patients experience from not having pain more than makes up for the academic discussion about this point. Moreover, on severe exertion they have substitution symptoms, discomfort in neck, choking sensation, pain in teeth, which put the brakes on maintaining the activity. They are, of course, cautioned about exertion as before operation and urged to limit it to what they can do without distress. Patients should not be chosen for this operation who have evidence of too marked damage to the heart muscle or who have had recent coronary occlusion, or who have heart failure.

There are several operations which are designed to increase the blood supply to the heart muscle. Beck<sup>39</sup> has tried pectoral muscle transplant and the production of adhesions by artificial means to bring in a new blood supply. O'Shaughnessy<sup>40</sup> brought vascular-rich omentum through an opening in the diaphragm and sutured it to the heart muscle. Thompson<sup>41</sup> has induced adhesions by the use of powder blown into the pericardial cavity. All of these measures are in the investigative stage and large numbers of patients should not be subjected to these procedures until further investigation has been made and the course of those already treated is known.

Another approach to the problem has been through the reduction of metabolic demands of the human organism by total ablation of the thyroid gland.<sup>42</sup> It is said to be effective in selected cases. More recently Raab has

reported<sup>43</sup> improvements in angina patients with the reduction of the basal metabolic rate from the administration of thiouracil. If this procedure proves effective and safe, it will avoid the disadvantages of a permanent defect brought about by surgical ablation of the thyroid gland.

The cervical rib and the scalenus anticus syndromes may be mentioned briefly. Pain in these syndromes may be confused with angina pectoris especially when the discomfort is on the left side. Relief may follow removal of the offending rib or cutting the muscle which encroaches upon the artery or brachial plexus. If hiatus hernia is the cause of pain, relief often follows from frequent small feedings and use of tincture of belladonna. A patient should not be treated for years for angina only to find later that he has hiatus hernia, spontaneous interstitial emphysema,<sup>44</sup> or ruptured thoracic disc. The exercise test, carried out with electrocardiographic records, and the Levy anoxemia test<sup>45</sup> are useful procedures in the differential diagnosis of angina pectoris.

*Treatment of the Irregularities of the Heart.* On the whole, I think irregularities of the heart have been managed in a more satisfactory manner in recent years.<sup>46</sup> What can be accomplished in the treatment of irregularities, per se, beyond the treatment of the underlying cause may be summarized as follows:

*A. Premature Contractions:* (1) Attention should not be directed to premature contractions if the patient is not aware of them. (2) When premature contractions give rise to symptoms, relief may be secured, frequently, by the use of small doses of triple bromide. (3) Auricular premature contractions may disappear on digitalization. (4) Ventricular premature contractions may occasionally require the use of quinidine.

*B. Paroxysmal Tachycardia:* (1) Supraventricular paroxysmal tachycardia may respond to simple measures like holding the breath, carotid sinus pressure, etc. (2) Mecholyl may cause cessation of supraventricular paroxysmal tachycardia. (3) Digitalization is the most satisfactory drug for treatment of auricular or nodal paroxysmal tachycardia. (4) Quinidine should be used for ventricular paroxysmal tachycardia. Digitalis should not be used in this rhythm and electrocardiograms should be taken when possible to be certain of the rhythm.

*C. Auricular Flutter:* (1) Digitalization will cause reversion to normal rhythm in most instances and is the drug of choice.

*D. Auricular Fibrillation:* (1) Digitalis should be used to keep the ventricular rate slow. (2) The following factors are to be considered in evaluation of the use of quinidine to cause reversion: (a) if the size of the heart is large, (b) if the duration of fibrillation is long, (c) if heart failure is present, quinidine should not be used for this purpose.

*E. Stokes-Adams Syndrome:* (1) Patients should be taught to live within their capabilities. (2) Adrenalin 1 c.c., 1:1000 solution, subcutaneously is the most effective drug. (3) I have recently seen complete heart block disappear with the use of ephedrine 20 mg. t.i.d.

*Arteriosclerotic Heart Disease.* Certain changes take place in the heart muscle and vessels with aging which occur early in some individuals and later in others. There are no means known of slowing the progression of these changes, aside from a rational mode of living and eating and engaging in activities. After the onset of symptoms referable to the heart, such as heart failure or angina, in this etiological group patients are treated by the means which are mentioned under those headings. By and large these patients have a longer, more comfortable and more useful life span ahead of them now than before the introduction of the mercurial diuretics.

*Coronary Occlusion.* What have we to offer the patient who has a coronary occlusion? With proper care I think the outlook need not be too depressing. Many patients return to full activity with some of their useless activities eliminated. It can be made a time for the individual to reassess his activities, aims in life, etc., and it has been my experience that these patients have often gone back to their profession or work with a clearer course, and a period of greater effectiveness than was theirs before this accident. I begin early in the attack to use the illness and convalescence as a period of reëducation from the point of view of the years to come. The acute period and the months afterward are the most important from the long time angle. I advocate the early use of oxygen when there are cyanosis and dyspnea and pain; I do not use vasodilator drugs except whiskey, and occasionally aminophyllin. There should be an adequate period of complete rest in bed, four to six to eight weeks or longer, depending on the severity and complications. During this time the bed pan is used; patients are fed; moderate, passive and then active movements of legs are made to prevent stasis; the position of body is shifted; breathing deeply several times a day expands the lungs; toward the end of the complete rest the head is propped up and then gradually the patient is brought to the sitting position, allowed to read, etc. Then, in order, very gradual sitting up, walking, lavatory privileges, bath, etc., requiring a month or more in getting to this stage; then gradual resuming activities one after the other, taking around five to six months before going back to work; and then gradual resumption of work. How much activity is finally attained depends upon the patient's cardiac reserve, economic status, interests, etc., and has to be carefully worked out with the patient. After about one year he is on his own again except for the periodic check-ups. In making these recommendations I am not unaware of the problems of the general practitioner, and realize how difficult it is to have patients adhere to this régime. Electrocardiograms aid in prognosis, since the anterior apex lesions have a somewhat more serious prognosis than do the posterior base ones.<sup>47</sup>

There is inadequate evidence offered by those who would have us treat coronary occlusion in an ambulatory or semiambulatory way to take this form of therapy seriously.<sup>48, 49</sup> The analogy between working a striated muscle to increase its blood supply and working the heart muscle in an area of which the blood supply is interrupted in a heart in which the arteries are

sclerotic and not normal, is not valid. Patients who have ignored the early symptoms of coronary occlusion, and have kept going, have done less well in my experience.

*Rheumatic Heart Disease.* What is the present status of what we can accomplish in rheumatic fever?

First, with respect to recurrences of rheumatic infection: there is nothing at present which can be offered the whole population of rheumatic fever patients to prevent recurrences. The use of sulfa drugs and perhaps eventually of penicillin to prevent streptococcal and respiratory infections has very interesting and far-reaching possibilities. The time is not yet ripe, in private practice, for putting patients on the drug with these objectives because the blood counts should be checked so frequently and blood levels of the drug followed. However, if anyone is interested in observing a series and keeping adequate records for the detection of toxicity, he should be encouraged. One gram of the drug a day appears to be adequate. Blood dyscrasias have been occasionally described in patients already subjected to this routine.<sup>50</sup> Increased impetus has been given to this problem by the studies made in the Army Air Force by Holbrook<sup>51</sup>; in this series there was a reduction in the incidence of rheumatic infection with the control of streptococcal infections with sulfadiazine. Proof of the prevention of recurrences by salicylates does not appear to be convincing enough to warrant their use. The prevention of recurrences by living in the tropics is applicable to the treatment of a relatively small number of patients.<sup>52</sup>

What can be done in the treatment of rheumatic patients with heart disease aside from the problem of recurrences: (1) Have the subject live a sane life, avoiding over exertion, etc. (2) Teach respect for colds and sore throats, advising bed rest during these episodes. Caution patient to avoid crowds in winter. (3) Use of sulfonamides before and after tooth extractions and tonsillectomies in order to prevent implantation of organisms causing subacute bacterial endocarditis. Sulfadiazine, 1.0 gm., together with soda bicarbonate 2.4 gm., q. 4 h. for the 24 hours before operation, the day of operation, and 48 hours after the procedure is recommended. If penicillin orally comes up to the early expectations, it may supplant sulfadiazine for this purpose. (4) The treatment and cure of subacute bacterial endocarditis with penicillin will be mentioned later. (5) Once the symptoms and signs of heart failure have appeared, there is now a more cheerful outlook with adequate treatment of failure so that maintenance of an adequate circulation over a longer time than was formerly to be expected is now possible.

*Luetic Heart Disease.* It is too early to estimate the effect which penicillin therapy will have on the incidence of luetic heart disease in later years.

*Heart Failure.* The onset of heart failure until fairly recently was viewed gloomily by physicians and patients. Digitalis was prescribed in a haphazard way, usually a few drops a day. As there was not spectacular improvement, the use of digitalis in the lay mind connoted the last stage of

their disease. The general principles of treatment of heart failure are the same whatever the etiological and anatomical background, whether rheumatic, arteriosclerotic, hypertensive, etc. Due to many factors the patient who has developed heart failure can now look forward to many years of usefulness with varying degrees of restriction of activities. The most important development, it seems to me, was the introduction of the mercurial diuretics. Next, and almost as important, has been the more intelligent use of digitalis. The general understanding is that larger amounts of digitalis must be given to get an adequate therapeutic effect, for instance, 1.8 gm. New York Heart Association preparation of digitalis may be given in 24 hours when the patient has not had digitalis within two weeks. The continued use of this drug by maintenance doses, the restriction of fluid intake to 1,200 c.c. q.d., and salt intake to 2 gm. q.d., the other adjuncts such as ammonium chloride, urea, and the restriction of the patient's activities after recovering from heart failure to what he can do without a recurrence, all contribute to maintenance of compensation. The most important phase of treatment of heart failure comes after recovery. It is still not uncommon to see all medication stopped after recovery and the patient allowed to resume the same amount of activity. It is much more important to prevent recurrence of failure than to treat each recurrence with the lessened capacity to restoration. After recovery from heart failure there should be slow convalescence, continuation usually of digitalis, continued use of mercupurin on every third day or at weekly intervals, continued restriction of fluid and salt intake, and adequate care about setting the level of the patient's activities. Today our cardiac patients continue to come to the clinic one to two times a week for years and years after the first onset of heart failure. Hazards in these patients are respiratory infections, especially acute bronchitis with the increased load on the heart; these should be treated with complete rest in bed, steam inhalations, often oxygen, etc. The treatment of heart failure by the use of large amounts of water and the acid ash diet as described by Schemm,<sup>52a</sup> requires further study before its use is widely advocated.

*Thyroid Heart Disease.* The appearance of cardiac complications in hyperthyroidism is well recognized. I am not referring to such manifestations as slight breathlessness and tachycardia, palpitation, rise in systolic blood pressure which are a part of the clinical picture. I refer to the appearance of auricular fibrillation, auricular flutter and heart failure. With the prolonged increase in basal metabolic rate the circulation is overburdened; there may be increase in breathlessness, râles, and all gradations of insufficiency up to marked congestive heart failure which does not differ in its clinical manifestations from other etiological types of failure. The treatment of decompensation is the same as in other patients with failure: namely, restriction of fluids to 1,200–1,500 c.c. q.d., low salt intake, full digitalization (1.8 gm. New York Heart Association preparation in 24 hours), mercupurin 2 c.c. intravenously every third day, oxygen tent if necessary; vitamin supplement may be used because there may have been depletion by the excessive



metabolic rate. If auricular fibrillation is present, it may require more than the usual amount to slow the ventricular rate, because of the increased basal rate. With the use of iodine (1 c.c. t.i.d. Lugol's solution or syrup of hydriodic acid) the heart rate slows, the symptoms regress, the patient gains weight, and there is reduction in the basal metabolic rate. There is with the use of all these measures reason to expect reduction or complete clearing of the signs and symptoms of heart failure and the patient can be made ready for operation. It is my custom to continue the use of maintenance amounts of digitalis in these patients through and past the postoperative period. In the presence of normal rhythm, at an appropriate time in convalescence if all has gone well, the reasons for further use are examined. If the rhythm is auricular fibrillation, I usually wait for some weeks after operation and in many, normal rhythm will recur spontaneously while digitalis is continued. If it persists the use of quinidine is considered, taking into account the absence or presence of heart failure, size of heart, duration of fibrillation.

In any patient in whom the onset of auricular fibrillation is not adequately explained, or in a patient with rheumatic heart disease with auricular fibrillation in whom the ventricular rate begins to be uncontrolled by the usual amounts of digitalis, with slight temperature rises, the onset of hyperthyroidism should be suspected. With close working together of surgeon and physician cardiac patients or hyperthyroid patients who have had heart failure can be safely carried through two stages of thyroidectomy under local or ether-oxygen anesthesia.

The place of thiouracil (1.0 gm. q.d. on the average) in the treatment of Graves' disease remains to be decided.<sup>53</sup> Careful observations of the white blood count should be made when the drug is being used. At the present time, in my opinion, it should not be used in complicated cases with cardiac manifestations. I think these patients can be managed better at present with iodine and operation until the effects of thiouracil are more clearly defined.

*Myxedema Heart.* The clinical picture of typical myxedema is easily recognized: the thick juicy, pasty skin, the pallor of the thick lips, the slowed down appearance, the mental dullness and slow speech, the cold skin,<sup>54</sup> coarse sparse hair, associated with a low basal metabolic rate, a high blood cholesterol, increased size of the cardiac shadow, a slow heart rate, and a history of gain in weight. The electrocardiogram shows low amplitude of the QRS-T waves, with varying degrees of auriculoventricular heart block.<sup>55</sup> The cardiac output in these patients is low per minute and per beat, the circulation time prolonged, the heart large, and the venous pressure usually normal.<sup>55</sup> With the administration of thyroid extract the patient improves objectively and subjectively. The basal metabolic rate increases, the heart shrinks in size, the cardiac output increases, and the circulation time becomes shorter, and the auriculoventricular block decreases and disappears.<sup>55</sup> These changes are reversible and can be made to swing in either direction by the use of or discontinuance of thyroid extract. The changes in heart size

are slower in taking place. We are very careful to give thyroid extract in small amounts and increase it gradually. For example to one of our patients we gave 0.015 gm. on February 24, increased to 0.03 gm. on March 3, to 0.06 gm. on March 7, to 0.10 gm. on March 15, to 0.12 gm. on March 21, and to 0.18 gm. on March 23. There is reason for not suddenly whipping up the circulation when it has been retarded for years. The danger of coronary occlusion in patients in this age group when demand is put on the circulation by increasing the metabolic requirements is very real.

*Beriberi Heart.* The occurrence of cardiac manifestations may be a part of vitamin B<sub>1</sub> deficiency, but clearcut instances of the so-called beriberi heart, such as were formerly encountered in the Orient, are not seen frequently. In this part of the country it is encountered as a part of chronic alcoholism associated with restricted food intake. There is enlargement of the heart with peripheral vasodilatation and moderate to generalized edema; the serum proteins may be low. Rapid arm to tongue circulation time in the presence of increase in venous pressure helps to differentiate this from the other types of heart failure.<sup>56</sup> The amplitude of the QRS complexes in the electrocardiogram may be decreased and occasionally there is negativity of T<sub>1</sub>. Prompt and rapid amelioration of all the signs and symptoms follows the daily administration of thiamin hydrochloride 50–100 mg. intravenously. Other measures such as use of whole wheat bread, lean meat, fresh vegetables, brewer's yeast may be instituted. If beriberi heart disease is suspected, digitalis and other diuretics should not be used not only because they are ineffective but also because they cloud the picture in making a correct diagnosis by the therapeutic test with thiamin.

*Anemia.* The cardiac embarrassment which may occur in severe anemia disappears with the increase in the red blood count and hemoglobin and restoration of the serum proteins.

*Acute Nephritis.* Occasionally heart failure may occur in acute nephritis and regress when the usual régime used in the treatment of heart failure is instituted.

*Acute Cor Pulmonale.* The acute embarrassment of the circulation which occurs with pulmonary infarction or overloading the heart with fluids is reversible. The clinical signs disappear and there is regression of certain typical electrocardiographic patterns which have been described in acute cor pulmonale.<sup>57, 58</sup>

*Thrombophlebitis and Pulmonary Infarction.* The treatment of thrombophlebitis has taken on new interest. The complications of thrombophlebitis which are feared are the formation of saddle thrombus, and of embolization to the lungs with a large embolus or with showers of emboli. When thrombophlebitis occurs in the leg veins, there are those who advocate prompt ligation of the vein under local anesthesia.<sup>59</sup> One of the most interesting advances in this field is in the use of anticoagulants. Heparin 30 to 40 mg. per hour in saline or 5 per cent glucose may be given by continuous intravenous drip, care being exercised to keep the clotting time within 20 to

30 minutes (not more than one hour). It may be kept up for one week to 10 days. It is best to use a concentrated solution so that not more than 1 liter of fluid is required in 24 hours. Prompt decrease in the swelling of the part results and the patient who was having repeated showers of pulmonary emboli recovers. I have had no experience with the use of dicoumarin as a substitute for heparin. Its effects are induced less rapidly and having been initiated they are less easily controlled because they are of longer duration, namely, one to five days. Its effect on the prothrombin time is observed.

It is my practice to attempt first the usual treatment of rest and elevation of the part with local dry heat, and if regression occurs, to maintain this régime. If, however, there is progression, use of the other measures is considered.

*Arterial Occlusions.* There is not a uniformity of opinion about the treatment of acute arterial occlusions and different surgeons seeing the same patient will recommend different procedures. If the patient is seen early and the vessel is large, embolectomy is to be considered. The other measures are the use of the Pavex boot, rocking bed, papaverine hydrochloride, 0.064 gm. q. 4 h. and lumbar paravertebral block of 2–3–4 with novocaine.<sup>60</sup> All of these measures are designed to enlarge the arterial blood supply and to promote the formation of collateral circulation. Without operation or nerve block I have seen return of excellent function from use of the Pavex boot and later, perseverance on the part of the patient in the use of the extremity.

*Subacute Bacterial Endocarditis.* I have reserved subacute bacterial endocarditis for final consideration. Until recently, after many years in Internal Medicine, I had yet to see a proved case of subacute bacterial endocarditis recover. One of the most encouraging gains in therapeutics in many years has been in the treatment of subacute bacterial endocarditis with penicillin. The use of sulfonamides often lowered the temperature and brought about sterilization of the blood stream for varying lengths of time. Recent analyses by White and Kelson<sup>61, 62</sup> as well as the experience of others has shown that very little was accomplished and its use has been abandoned. On the other hand, the results which have been reported from the use of penicillin are very encouraging,<sup>63</sup> and additional reports are appearing rapidly from many clinics. With proper treatment, *at least* 50 per cent or more of early cases of subacute bacterial endocarditis are cured. It is too early, however, to have gained any definite notion about what the percentage of cures will ultimately be, and what the life history of those cured will be. The diagnosis should be substantiated by positive blood culture and tests should be made to assay the sensitivity of the strain of organism to penicillin. If it is sensitive, penicillin should be given. Rapid strides are being made in the technic of penicillin therapy and routines of therapy have not become shaped. It appears at present that 300,000 to 400,000 units daily, given q. 2 h., intramuscularly day and night continued for several weeks is the technic of choice. There is little evidence that anything is gained by

giving heparin simultaneously, as described by Loewe. Extremely large doses up to 1,000,000 or 5,000,000 units a day may be required to sterilize the blood stream. After recovery from subacute bacterial endocarditis the underlying heart disease remains with its implications.

### SUMMARY

In evaluating the present status of the treatment of cardiac diseases we find that we are in a period of rapid advancement. Advances have been contributed by surgical measures for treating cardiac abnormalities, and by new chemotherapeutic measures and new drugs and refinements in the use of other well known drugs. Moreover, there is still room for the continued utilization of the art of medicine in the management of sick individuals. Patients with hopeless congenital cardiac defects, formerly thought beyond relief, are now restored to normal health; patients with hearts restricted by encasement in unyielding fibrous tissue which may be calcified, with progressive invalidism facing them, are restored to normal activity; patients with the hopeless prognosis of subacute bacterial endocarditis are apparently cured; and patients who have heart failure now maintain an effective cardiac reserve with the intelligent use of digitalis and mercurial diuretics and attain a longer, more comfortable and more useful life span. These triumphs, to recapitulate only a few, give us ample encouragement to look to the future with confidence that further advances are to be expected.

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# AN APPARATUS FOR THE INTRODUCTION OF PENICILLIN AEROSOL INTO THE NASAL ACCESSORY SINUSES WITH A CASE REPORT OF A PATIENT WITH CHRONIC SINUSITIS \*

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IN a preliminary report <sup>1</sup> the inhalation of nebulized penicillin in broncho-pulmonary infections was described. In some instances the mist of penicillin was inhaled through the nose with the idea that the sinuses might be in communication with the air in the nasal passages. However, in order to introduce penicillin aerosol into the sinuses, it was finally considered necessary to evacuate air from the sinuses by developing a negative pressure in the nasal passages with immediate replacement of air containing penicillin in high concentrations.† ‡

An apparatus was devised for production of penicillin aerosol with intermittent negative pressure in the nasal and postnasal pharynx. A glass venturi tube was inserted in the rubber tubing from the oxygen cylinder. The lower end of the venturi tube was connected by rubber tubing to the re-inhalational nebulizer. With a liter flow from the oxygen regulator set between 6 to 12 liters per minute a satisfactory production of penicillin aerosol is obtained. The horizontal glass tube of the venturi is connected to a positive and negative pressure valve (figure 1). The purpose of this especially constructed valve is to allow the passage of oxygen through the nebulizing apparatus when the handle is in the upright position and to develop a negative pressure in the nose pieces when the handle is in the horizontal position. When suction is being produced in the nasal cavities oxygen flows through an aperture in the valve and is prevented from going through the nebulizer. When the handle of the valve is turned to the upright position a negative pressure in the nasal cavities is stopped and the oxygen stream is then diverted to the nebulizer reinhalation apparatus. The details

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† We are indebted to Dr. George Foster Herben for suggesting the preliminary use of suction in combination with the penicillin reinhalation apparatus.

‡ Reduced atmospheric pressure in a low pressure chamber has been used with favorable results to provide effective suction and increase aeration of the sinuses and promote drainage.<sup>2</sup> During the period when air reenters the nasal accessory sinuses no antibiotic substance was used in this procedure.



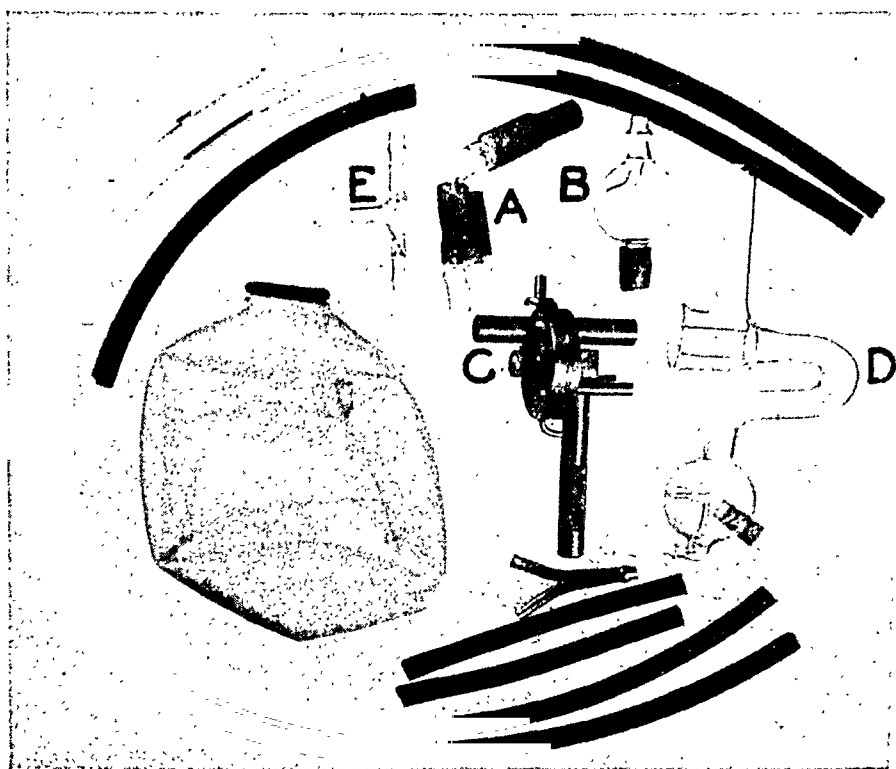
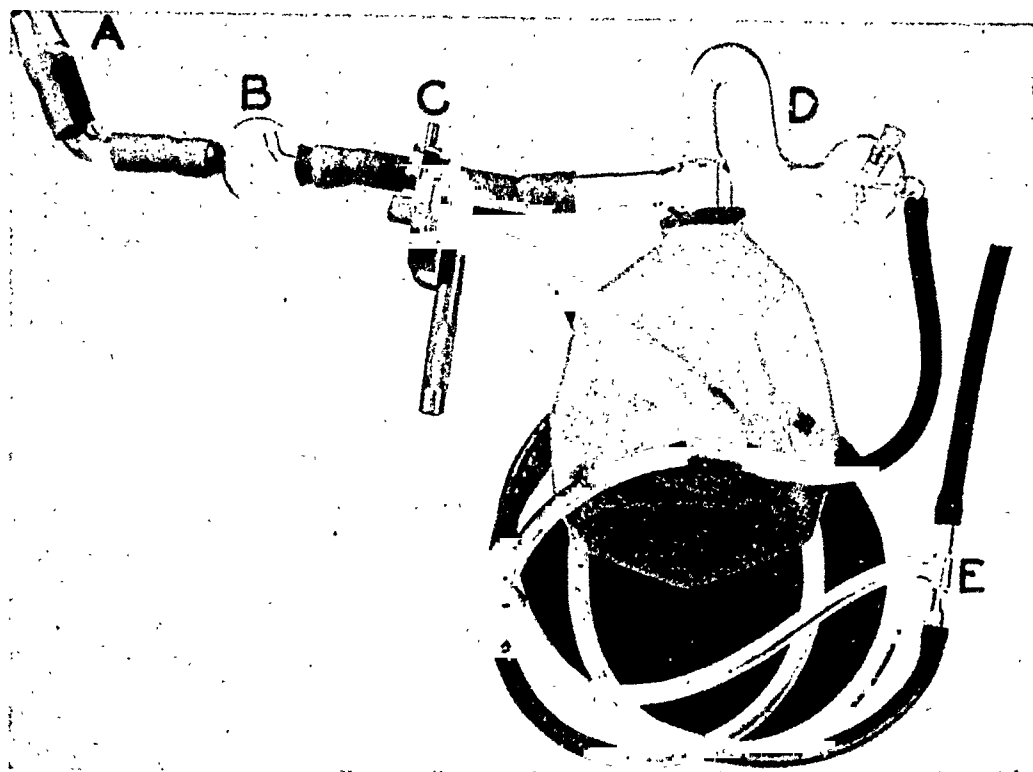


FIG. 1. A reinhalational nebulizer apparatus with a positive and negative pressure valve attachment for the introduction of penicillin aerosol into the nasal accessory sinuses: (A) Nose piece, (B) glass trap for collection of nasal secretions, (C) special valve for provision of positive and negative pressures; horizontal position produces suction, upright position connects nebulizing apparatus with nose piece for inhalation of penicillin, (D) reinhalational nebulizer, (E) venturi tube for production of negative pressure.

of the mechanism of the positive and negative pressure valve are illustrated in figure 2.

Although the conventional positive and negative pressure nose and throat apparatus may be employed with the special valve illustrated above (figure 2), the glass venturi tube inserted in the tubing from the oxygen cylinder produces completely adequate suction as well as positive pressure and has the advantage of use by the patient in his own room. The degree of negative pressure obtained at the orifices of the nasal attachment depends on the rate of flow of oxygen through the venturi tube. As will be seen in table 1 negative pressures of considerable degree are produced when the oxygen flow is between 7 and 10 liters per minute.

#### POSITIVE AND NEGATIVE PRESSURE VALVE

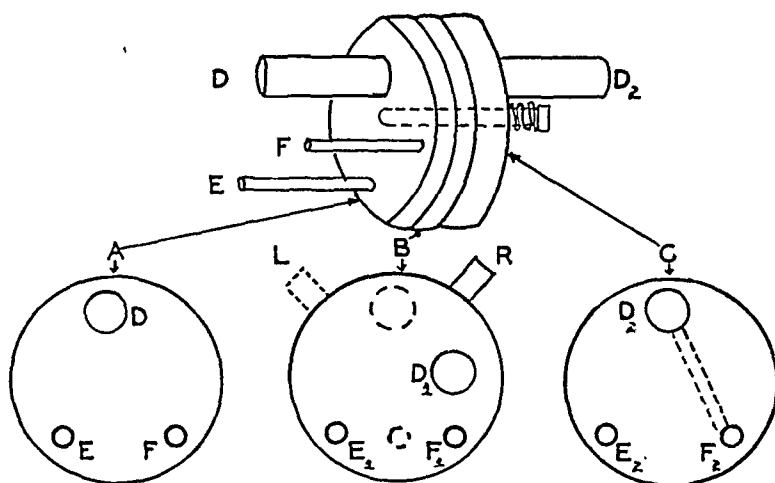


FIG. 2. Positive and negative pressure valve. The valve consists of three discs A, B, and C held together by a spring and having three holes D, E, and F. The outer discs are yoked together and the center disc B may be rotated 30°. Positive pressure leads are attached to D and E. Negative pressure lead is attached to F. D<sub>2</sub> is attached to nose piece. When center disc is moved to left hand position D, D<sub>1</sub> and D<sub>2</sub> are in line and E and F are occluded. When center disc is moved to right hand position E lines up with E, and E<sub>2</sub>, F with F, and F<sub>2</sub> and D is occluded. In this position negative pressure is applied to D<sub>2</sub> through a channel from F<sub>2</sub>.

The purpose of this procedure is to introduce air containing penicillin into the nasal accessory sinuses after partial evacuation of air or secretions from the sinuses have been obtained by negative pressure in the nasal passages. At the start of a treatment the nose pieces are fitted snugly into the nose, the handle of the special valve is turned upward and the oxygen flow set to 8 liters per minute. The patient then breathes penicillin aerosol for one to three minutes. The solution employed consists of a concentration of 20,000 to 25,000 units of penicillin per c.c. of normal saline. Since the nebulizer employed produces particles of small size, the majority of which are under 1 micron in diameter, the mist is relatively stable and does not quickly condense in the rebreathing bag.\* After a preliminary period of inhalation

\* The reinhalation nebulizer has been made from the Vaponefrin type nebulizer.

of penicillin nebulin through the nose has been performed the handle of the special valve is turned downward and the patient is instructed to say K-K-K until a definite suction effect is experienced. In our experience swallowing has been more effective in producing a negative pressure in the nasal passages than the use of the K maneuver. After several suction effects have been obtained the handle of the valve is turned to the upright position and penicillin aerosol is again inhaled. This procedure is repeated until 2 c.c. of the solution has been nebulized. In this way repeated evacuation of air from the sinuses and replacement with air containing a mist of penicillin is produced. During the phase of negative pressure the Eustachian tube may be opened in those cases in which previous obstruction has been present.

Previous shrinkage of the mucous membrane of the nose may be obtained with either neosyneprine or privityne. In addition the nasal passages may be

TABLE I  
Negative Pressure Produced by Oxygen Flow Through Venturi Tube

Oxygen Flow, Liters per Minute	Negative Pressure, cm. Hg
3½.....	2
4½.....	4
5½.....	6
6½.....	8
7½.....	11
8½.....	14
9.....	16
10.....	18.2
11.....	21
12.....	22
13.....	23.4
14.....	24.4
15.....	26

first cleansed by washing with normal saline or saline containing penicillin, 500 U/c.c. Neither of these procedures is generally used.

In order to prevent secretions from the nose entering the valve a glass trap has been inserted between the nose piece and the valve.

The number of treatments with intermittent negative pressure and penicillin aerosol inhalation will have to be determined by experience and the indications of the individual patient. In previous investigations of bronchopulmonary infections an inhalation of 50,000 units, at times 100,000 units, in 1 c.c. normal saline, was employed four to five times daily, often in conjunction with an oral dose of 100,000 units of penicillin at bedtime and during the middle of the night. The dosage of penicillin in the therapy of chronic pan-sinusitis requires considerable further investigation.\*

\* In hospital practice, four treatments are given daily, 40,000 units of penicillin in 2 c.c. normal saline. When the patient breathes through the mouth during the nebulization of penicillin, a more dense mist is present in the nasal passages. A single daily treatment has been used in office treatment, generally 50,000 units in 2.5 c.c. normal saline. The nebulizer should be rinsed three times with 0.5 c.c. normal saline, in order to dissolve the penicillin that clings to the glass walls of the nebulizer. This solution is then nebulized, with intermittent negative pressure.

The purpose of this report is to present a method by which a negative pressure may be produced in the nasal cavity that might accomplish drainage and partial evacuation of air in the accessory nasal sinuses, and in addition introduce penicillin aerosol into the sinus cavities themselves. Although a concentration of 50,000 units per c.c. would be irritating if applied locally in a solution, the provision of this concentration in the form of a nebulin exercises a different effect since particles of 1 micron or less lodge on the mucous membrane of the nose or sinuses and are immediately surrounded by a fluid medium that swiftly results in a dilute concentration. Calcium penicillin has been found to be better tolerated and much less apt to cause irritation than the sodium salt.

The following case was treated by a combination of orally administered penicillin and intermittent negative pressure with penicillin aerosol inhalations.

#### CASE REPORT

*History.* A 15 year old white school boy had a history of chronic sinusitis dating back to infancy, following an attack of bilateral acute otitis media with spontaneous perforation of both drums. A second episode occurred at the age of two and one-half years with accompanying mastoiditis not requiring surgery. Since that time the patient had had chronic purulent nasal and aural discharge. Two years previous to admission, following a severe case of measles, he developed bilateral deafness which persisted for two months and left some permanent impairment. Adenoidectomy was performed at the age of 11 months, tonsillectomy and adenoidectomy at the ages of 7 and 13 years. For many years the patient had undergone frequent ear, nose and throat treatments with antral irrigations and inflation of the Eustachian tubes with little improvement. His complaints on admission were impaired hearing, nasal discharge with stuffy sensations, occasional non-productive cough, easy fatigability, and four pounds weight loss in recent months. He denied headaches, otalgia and fever.

*Physical Examination.* The patient was a well-developed, fairly well-nourished white youth not appearing ill. Temperature 98.6° F., pulse 80, respirations 20, blood pressure 108 mm. Hg systolic and 70 mm. diastolic. Positive findings were limited to ear, nose and throat examination. Nose revealed slight deviation of the septum to the left, a boggy congested mucosa with a small amount of mucopurulent discharge in both nostrils and hypertrophy of the inferior turbinates. There was obvious impairment of hearing, more marked on the right. Bone conduction was greater than air conduction. Weber test did not lateralize. There was slight yellowish discharge filling the external auditory meatus bilaterally. Pharynx appeared moderately reddened. The posterior cervical lymph nodes were slightly enlarged but non-tender.

*Laboratory Data.* Hemoglobin 14.8 gm., red blood cells 5.2, white blood cells 5,700 with polymorphonuclears 46 (0-6-40), lymphocytes 46, monocytes 7, eosinophiles 1. Sedimentation rate 5 mm./hr. Sputum culture: *Staphylococcus albus* predominating. Nasal culture: no growth. Sinus roentgenograms revealed clear frontals, bilateral clouding of the ethmoid cells; marked thickening of the lining membrane of both maxillary antra with homogeneous density in the lower half suggesting fluid present, and peripheral clouding of the sphenoids suggesting thickened lining membrane (figure 3, left).

*Course.* The patient remained afebrile throughout his two weeks' stay and was ambulatory. He was treated with a course of oral sodium penicillin, 100,000 units

mixed with 10 c.c. amphojel five times daily, receiving a total of 5,900,000 units. Calcium penicillin aerosol was administered by nasal inhalation using the alternating negative and positive pressure apparatus with a dosage of 50,000 units in 1 c.c. normal saline two to three times daily for a total of 1,100,000 units. No other drugs or therapy were employed. By the third day of this regimen the patient noted marked improvement which was sustained. Nasal discharge practically disappeared and the mucosa appeared healthy. There was concomitant improvement in hearing and the patient's general sense of well-being. Sinus roentgenograms after one week of treatment showed definite clearing of the ethmoid and antral sinuses, although some thickening of the antral lining membranes persisted. Sinus films 11 days after the

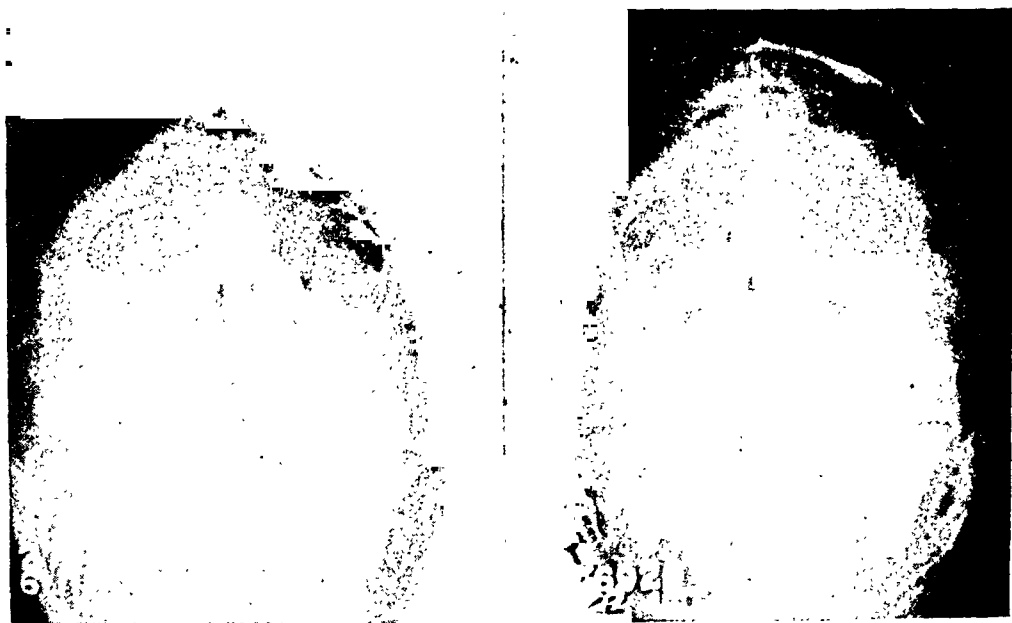


FIG. 3. Roentgen-ray examination of the sinuses before treatment (June 11, 1945) revealed bilateral clouding of the ethmoid cells, marked thickening of the lining membrane of both maxillary antra with homogeneous density in the lower half suggesting a fluid level and peripheral clouding of the sphenoids suggesting thickened lining membrane. Sinus films 11 days after the onset of therapy (June 22, 1945) showed definite clearing of the ethmoid and antral sinuses with no evidence of retained fluid.

onset of therapy showed further improvement in appearance of maxillary antra and ethmoid cells with no evidence of retained fluid (figure 3, right). Throat culture following treatment revealed *B. aerogenes* predominating. The patient was discharged from the hospital markedly improved.\* †

\* This patient remained entirely well, without nasal discharge, for eight months. Although he then developed an acute coryza, he recovered without flare-up of sinus infection. Subsequent roentgenograms showed no sinus disease. His hearing and general health are much improved.

In four other cases of severe sinus disease, nebulized penicillin with negative pressure resulted in clearing of the infection, without the use of oral or systemic administration of penicillin. Our more recent experience is highly encouraging, suggesting that the procedure described above is not only a valuable therapeutic aid in the treatment of sinusitis, but one that is free from pain and trauma and easily carried out in the office, hospital or home.

† The negative pressure valve set-up used in the treatment of sinusitis may be obtained from F. F. Anderson & Co., 4652 Spuyten Duyvil Parkway, New York, 63, N. Y.

## SUMMARY

An apparatus is described which provides: (1) negative pressure in the nasal passages and nasal accessory sinuses, (2) inhalation of nebulized penicillin, and (3) partial evacuation of air from the sinuses and replacement with penicillin aerosol.

A venturi tube attached to the oxygen regulator produces an adequate negative pressure when a flow of 6 to 10 liters per minute of oxygen is used.

A specially constructed valve, attached to a reinhalation nebulizer, makes possible alternate inhalation of penicillin aerosol and suction-pressure in the nasal cavities and accessory sinuses.

A case of chronic sinusitis is reported in which marked improvement took place following a combination of orally administered penicillin and intermittent negative pressure with penicillin aerosol inhalations.

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# CASE REPORTS

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## ACUTE HEMOLYTIC ANEMIA DUE TO NEOARSPHENAMINE: REPORT OF A FATAL CASE \*

By LAWRENCE E. YOUNG, M.D., WILLIAM N. VALENTINE, Lieutenant, M.C.,  
A.U.S., and JOE W. HOWLAND, Lieutenant, M.C., A.U.S.

A CASE of fatal hemolytic jaundice following injection of neoarsphenamine is described in this report. No descriptions of similar reactions can be found in the literature.

Moore<sup>1</sup> states that "the relative rarity of the blood dyscrasias due to the arsenical drugs is fortunate, since they are among the gravest of treatment complications." He points out that in more than half of the reported cases the blood picture was that of aplastic anemia and 80 per cent of these patients died. Farley<sup>2</sup> expresses the belief that all blood dyscrasias after arsphenamine therapy are manifestations of varying degrees of depressed bone marrow activity. Although aplastic anemia, agranulocytosis and thrombocytopenia have been repeatedly described as complications of the arsenical treatment of syphilis, there is to the best of our knowledge, no record of the occurrence of hemolytic anemia after the administration of any of the arsphenamines.

Dameshek and Schwartz<sup>3</sup> list arsphenamine and neoarsphenamine among the causes of hemolytic anemia but give no reference to specific cases. Dameshek<sup>4</sup> does not cite any specific instances of hemolytic reaction following arsenotherapy, and this type of hematologic complication is not mentioned in the reviews of Loveman,<sup>5</sup> McCarthy and Wilson,<sup>6</sup> Hahn,<sup>7</sup> Phelps,<sup>8</sup> and Probey et al.<sup>9</sup> Carter, Chambers and Anderson,<sup>10</sup> in their report of 1,153 reactions after 1,900,000 doses of arsenicals, describe a case in which death followed injection of silver arsphenamine. The autopsy diagnoses include multiple hemorrhages, aplastic anemia and acquired hemolytic jaundice. However, no clinical or pathological data are given to support the diagnosis of hemolytic jaundice. The liver is described as being browner than normal and having "indistinct internal markings" but no mention is made of the findings in the blood serum or urine (other than hematuria). The blood picture presented is that of aplastic anemia.

The case described in this paper is presumably the first of its kind to be reported.

### CASE REPORT

F. G., a 54 year old Italian male, was admitted to the Strong Memorial Hospital at 1:00 a.m., July 31, 1943. Three hours before admission he had been given 0.4 gm. neoarsphenamine intravenously by his private physician. Five minutes after receiving the injection he became violently dizzy and had severe chilly sensations. When he reached home he vomited twice and then began to have severe pain in the lower back.

\* Received for publication October 31, 1944.

From the Department of Medicine, The University of Rochester School of Medicine and Dentistry and the Medical Clinic of the Strong Memorial Hospital.

He was then seen by his physician, given adrenalin without relief, and sent to the hospital.

The past history with reference to syphilis and antisyphilitic therapy is summarized in table 1. He received his first injection of neoarsphenamine in 1940 and the second and third injections on July 9 and 16, 1943, without reaction. The fourth dose of neoarsphenamine was given July 23, 1943, and was followed immediately by chills and fever and a 12 hour episode of nausea and vomiting. During the next week he was apparently normal and worked as usual. The symptoms described above followed the fifth injection of neoarsphenamine on July 30, 1943.

TABLE I  
Luetic History of Case Reported

Date	Number of Injections of Anti-luetic Drugs <sup>1</sup>				Reactions to Therapy	Serological Tests of Blood for Syphilis	
	Bis-muth <sup>2</sup>	Ars-phen-amine <sup>3</sup>	Neo-arsphen-amine	Ma-pharsen <sup>4</sup>		Wasser-mann <sup>5</sup>	Kahn
1924	History of Penile Chancre						
1928						4+	3+
1928-1934	Type of Treatment Unknown						
1934-1940	90	80			Chills and Fever for 3 Days after Bi Injection in 1940	2+	4+
Dec. 7, 1940			0.2 Gm.		None		
Dec. 14, 1940 to April 1941				15	None	-	+
Feb. 6, 1943				1	None	Spinal Fluid Negative	
Mar. 1943 to July 1943	8				None		
July 9, 1943			0.1 Gm.		None		
July 16, 1943			0.2 Gm.		None		
July 23, 1943			0.3 Gm.		12 Hour Episode of Chills, Fever, Nausea and Vomiting Starting Immediately after Injection		
July 30, 1943			0.4 Gm.		Acute Hemolytic Reaction		
August 1, 1943	Autopsy: Syphilis of Aorta and Aortic Valve						

<sup>1</sup> All anti-luetic therapy was administered outside the Strong Memorial Hospital.

<sup>2</sup> Bismuth subsalicylate 0.13 gm. in 1.0 c.c. peanut oil intramuscularly.

<sup>3</sup> Arsphenamine dosage: 0.2 to 0.4 gm. intravenously.

<sup>4</sup> Mapharsen dosage: 0.02 to 0.03 gm. intravenously.

<sup>5</sup> Cholesterinized antigen.



*Physical Examination.* On admission the temperature was 103° F., pulse 160, respirations 28 per minute, blood pressure 90 mm. Hg systolic and 55 mm. diastolic. The patient appeared acutely ill and the skin was hot, dry and flushed but no rash was present. The tongue was dry and partially coated with blood that appeared to have oozed from the gums. Cardiac findings were normal except for marked tachycardia. The lungs were clear. Abdominal and neurological examinations were negative. A penile scar was present.

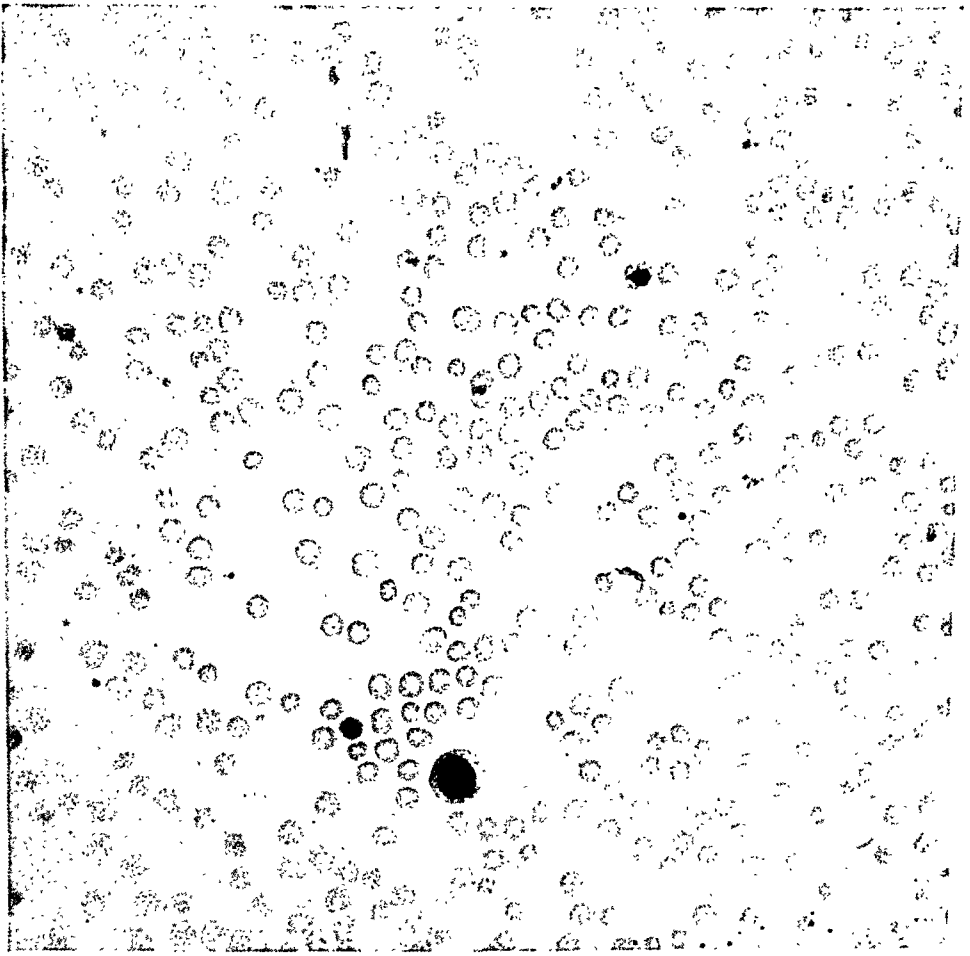


FIG. 1. Blood smear showing an undifferentiated white cell, two normoblasts, moderate anisocytosis of the red cells, and a few spherocytes.

*Laboratory Findings.* The urine was reddish brown, contained many golden brown granular casts, a few white blood cells but no red blood cells. The guaiac test for hemoglobin, and the heat and acetic acid test for albumin were strongly positive. The foam test for bilirubin was negative.

The blood plasma was reddish brown and had a hemoglobin content of 370 mg. per 100 c.c. The icterus index was 40, carbon dioxide combining power 35 volumes per cent, non-protein nitrogen 47 mg., albumin 4.2 grams and globulin 1.8 grams per 100 c.c. The red blood cell count on admission was 3.5 million,\* white blood cell count 4,800, hemoglobin 13.4 gm., reticulocyte count 3 per cent. A blood smear

\* A possible explanation of the relatively high red blood cell count may be found in the presence of the shock state with its known hemoconcentration.

(figure 1) prepared at 1:00 p.m. on July 31 and stained with Wright's stain showed moderate anisocytosis, and slight poikilocytosis. A few spherocytes were seen. The average red cell size was estimated to be normal. There was some stippling and diffuse basophilia of the red cells, and 10 normoblasts per 100 white cells were counted. Platelets were present in normal numbers. No toxic granules were seen in the neutrophils, but there was a shift to the left and an eosinophilia of 8 per cent. A differential count of 200 white cells was as follows:

Basophiles.....	0.5%	Stab cells.....	24.0%
Eosinophiles.....	8.0%	Filamented cells.....	10.0%
Myelocytes.....	1.5%	Lymphocytes.....	34.5%
Juveniles.....	20.0%	Monocytes.....	1.5%

The results of the erythrocyte fragility test (hypotonic saline) are given below.

	Per Cent Sodium Chloride Giving Indicated Degree of Hemolysis		
	Beginning	Marked	Complete
Patient.....	0.52%	0.40%	0.30%
Control.....	0.48%	0.40%	0.32%

Tests for cold agglutinins, cold hemolysins (Donath-Landsteiner) and warm hemolysins were negative. Attempts to demonstrate hemolysis of the patient's cells in

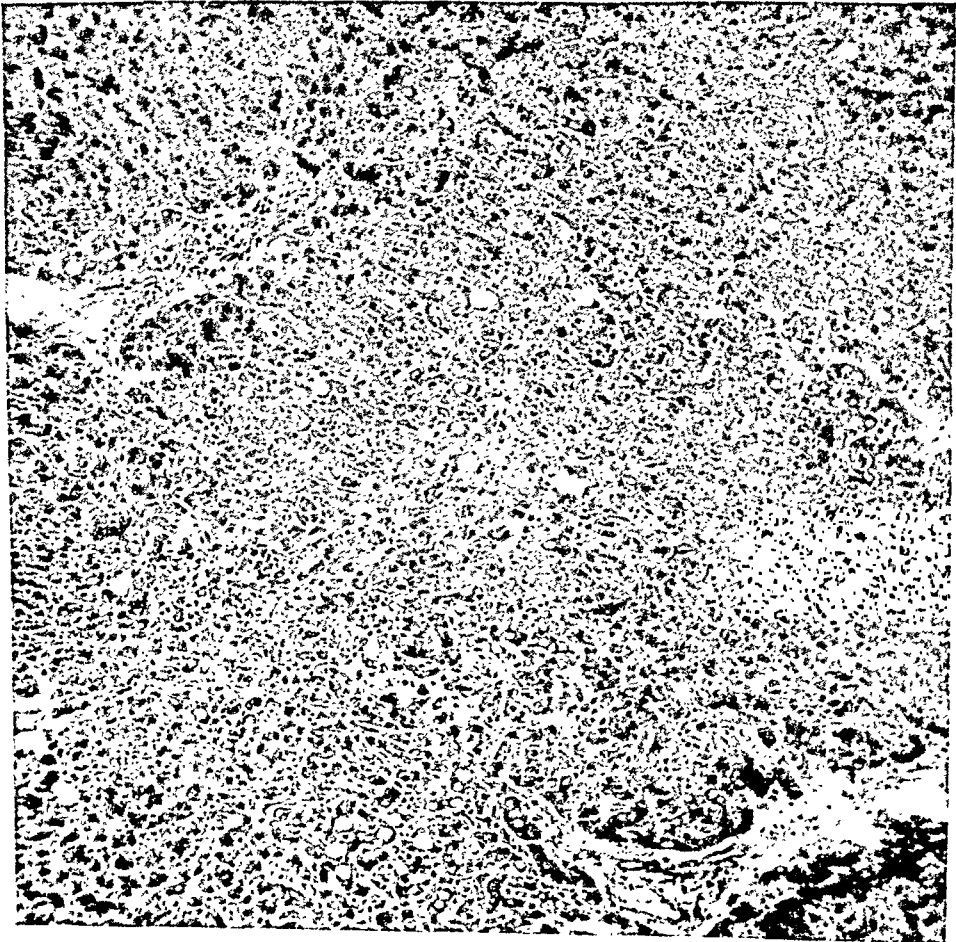


FIG. 2. Section of liver showing focal necrosis and vacuolization of liver cells.

mixtures of compatible normal serum and various amounts of neoarsphenamine were unsuccessful.

*Course in the Hospital.* During the patient's 24-hour stay in the hospital only 80 c.c. of urine could be obtained by catheterization. The temperature remained elevated and the blood pressure rose to 116 mm. Hg systolic and 80 mm. diastolic a few hours after admission, but later fell to 70 mm. systolic and 60 mm. diastolic and could not be obtained during the last half hour of life. Within 12 hours after admission the sclerae became icteric and the liver was palpable.

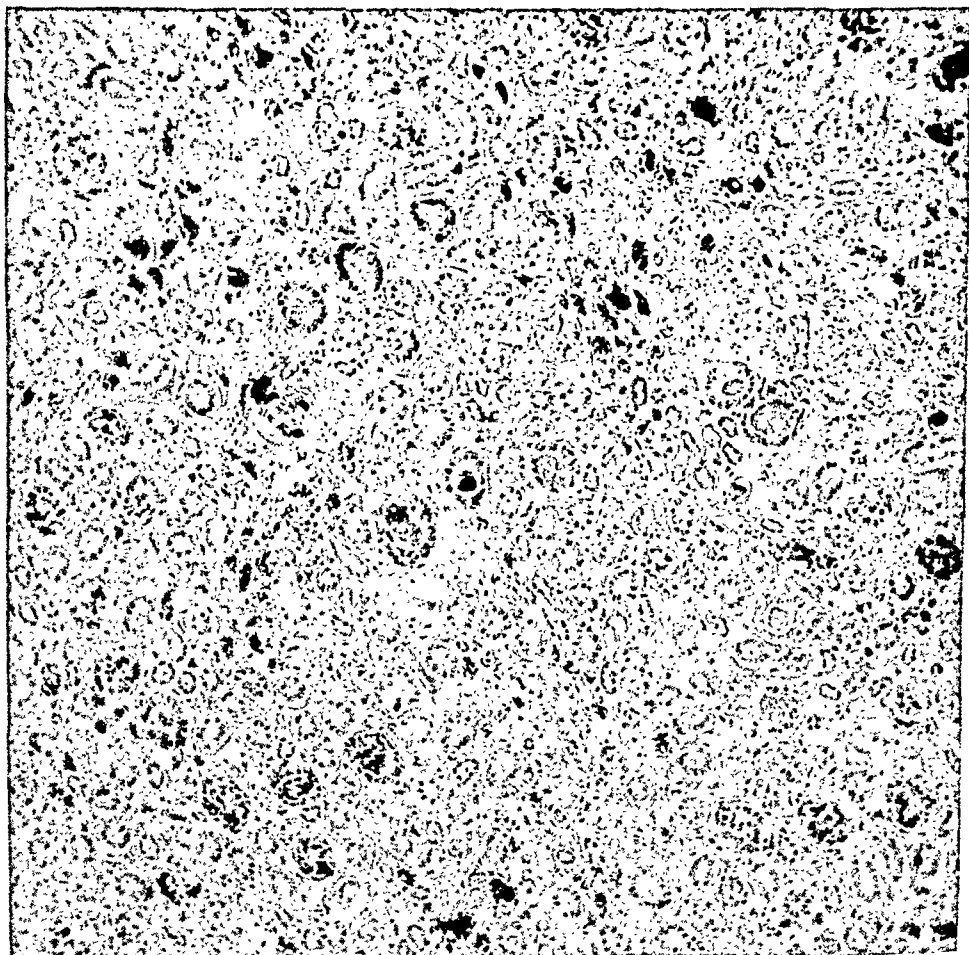


FIG. 3. Section of kidney. Hemoglobin casts are present in some of the collecting tubules.

Therapy consisted of sodium lactate, dextrose and blood plasma given intravenously in an attempt to promote diuresis and combat shock. Pulmonary congestion developed terminally and the patient became dyspneic, cyanotic and died at 1:20 a.m., August 1, 1943. The necessary vigorous intravenous therapy undoubtedly contributed to the development of the terminal pulmonary edema.

*Autopsy Findings.* There was minimal syphilitic involvement of the aorta and aortic valve. Hydrothorax and pulmonary congestion and edema were present bilaterally. In the liver (figure 2) were focal areas of hyaline necrosis and infiltration with neutrophilic granulocytes. Some of these areas were located centrally, some peripherally in the lobule; most of them occupied about one-third to one-half of a

lobule but some replaced an entire lobule. The other liver cells contained an increased number of large and small vacuoles.

The spleen was intensely congested and there were numerous polymorphonuclear leukocytes in the red pulp. There was dense infiltration of the adrenal medulla with lymphocytes and a few polymorphonuclear cells.

The convoluted tubules of the kidney showed cloudy swelling in some areas; in others the tubular cells were entirely degenerated and only granular, pink-staining material remained in the tubule. Some of the collecting tubules contained hemoglobin casts (figure 3).

The bone marrow showed a moderate degree of normoblastic hyperplasia.

### DISCUSSION

Further consideration of this case involves the answers to two questions.

1. Was the fatal illness caused by the injection of neoarsphenamine or was it merely coincidental? It should be emphasized that a milder but unmistakable reaction occurred immediately after the fourth injection of the drug one week prior to admission and that symptoms of the fatal reaction began within five minutes after receiving the fifth and last injection. This sequence of events and the eosinophilia of 8 per cent suggest a specific sensitization as the basis for the reaction. In view of this history and the fact that other drugs of similar chemical composition are known to cause hemolytic anemia,<sup>3</sup> the conclusion that death was due to neoarsphenamine seems reasonable.

The question might be raised as to the presence of a subclinical form of congenital hemolytic jaundice with a crisis precipitated by the drug. Against this remote possibility are the lack of significant increase in fragility of the erythrocytes in hypotonic saline, the absence of hemosiderosis in the liver and spleen, and the negative history of jaundice and anemia in other members of the family. With regard to the presence of spherocytes in the patient's blood smear, it can only be said that these cells are found in acquired hemolytic anemia as well as in the congenital type.<sup>3</sup>

2. Was the anemia truly hemolytic in nature? The hemoglobinemia and hemoglobinuria indicate that red cells were being destroyed rapidly. Accelerated activity of the marrow was clearly shown by slight reticulocytosis, basophilia of the erythrocytes, normoblastic hyperplasia of the marrow and the presence of normoblasts in the peripheral blood, as well as by the shift to the left in the granulocytes. It is clear that this was not a case of aplastic anemia. It is well known that most of the drugs capable of causing hemolysis *in vivo* do not do so in the test tube. Hence, it is not surprising that all of the tests for hemolysis performed were negative.

The renal lesions are similar to those described after acute hemolytic reactions from a variety of causes, including the transfusion of incompatible blood.<sup>11</sup> Although severe renal damage after arsenotherapy in the absence of excessive blood destruction has been described,<sup>1,7</sup> it seems more likely that the pathologic changes seen in this case were caused by the hemolytic reaction rather than by any direct toxic effect of the neoarsphenamine itself.

Two explanations of the mechanism by which focal necrosis of the liver was produced seem reasonable. (1) Lesions similar to those shown in figure 2 have been observed in patients suffering from hemolytic processes of various types.<sup>11, 12</sup> That some product of the rapid destruction of erythrocytes may cause this injury

is also suggested by the studies of Hawkins et al.<sup>13</sup> who repeatedly observed necrosis of the liver followed by death in dogs injected intravenously with alkaline hematin solutions. (2) It is known that the arsphenamines themselves are capable of producing all degrees of parenchymatous hepatic degeneration.<sup>1, 14</sup> Although it is obviously impossible to solve the mystery of pathogenesis of the hepatic lesions in this case, it is probably fair to state that the patient's jaundice was of the hemolytic or "retention" type rather than "regurgitative"<sup>15</sup> because of the absence of bilirubin in the urine. Another type of postarsphenamine jaundice can therefore be added to the list of those previously described.<sup>14, 16, 17, 18</sup>

### SUMMARY

A case of fatal hemolytic anemia following the fifth injection of neoarsphenamine is described. No earlier reports are known.

The hepatic and renal lesions appear to be the result of the hemolytic reaction rather than of the toxicity of the neoarsphenamine.

Hemolytic jaundice should be included in the classification of postarsphenamine jaundice.

The authors are indebted to Dr. John S. Lawrence, Dr. William B. Hawkins and Dr. Sidney C. Madden for assistance in the preparation of this report.

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## THE SYNDROME OF COMPRESSION OF THE PULMONARY ARTERY BY A SYPHILITIC AORTIC ANEURYSM WITH OR WITHOUT ARTERIO-ARTERIAL COMMUNICATION \*

By I. C. BRILL, M.D., F.A.C.P., and R. S. JONES, M.D., *Portland, Oregon*

It is well-known that simple syphilitic aortic aneurysm imposes no appreciable strain on the heart. If heart failure supervenes it is usually found to be due either to involvement of the aortic valve or to narrowing of the coronary ostia. In both these instances the strain is predominantly on the left ventricle and is recognized clinically by left-sided enlargement with aortic configuration and electrocardiographic changes denoting left ventricular preponderance.

A much rarer complication of aortic aneurysm is compression of the pulmonary artery with or without arterio-arterial communication. The cardiac strain in this instance is predominantly of the right ventricle. The rarity of this complication is evident from the fact that up to the present time (1944) only 86 cases have been recorded in the literature, of which only six were recognized during life. For detailed reports of these cases together with a review of the literature, the reader is referred to recent publications by Garvin and Siegel,<sup>1</sup> White, Chamberlain and Kelson,<sup>2</sup> Porter,<sup>3</sup> Schattenberg and Harris,<sup>4</sup> and Nicholson.<sup>5</sup>

The purpose of this communication is to place on record an additional case diagnosed during life and to point out two possible sets of symptoms and signs the recognition of which should permit more frequent clinical diagnosis of the condition.

### CASE REPORT

F. G., a white laborer, aged 52 years at the time of his death in January, 1944, was first seen in the Out-Patient Clinic 10 years previously (September, 1933) for an acute upper respiratory infection. A history was obtained of an untreated penile sore contracted at the age of 18 and the blood showed a four plus Wassermann reaction. Physical examination revealed no noteworthy changes; the heart was normal in size and shape and the cardiac sounds were unaltered. The patient was treated intensively with bismuth and neoarsphenamine from September, 1933, to October, 1939, during which period several physical examinations revealed no significant changes until April 6, 1937, when a "distant diastolic murmur along the lower left sternal border" was found. On that same day fluoroscopic examination showed no cardiac enlargement and the aortic shadow was considered normal.

\* Received for publication February 19, 1945.

From the Departments of Medicine and Pathology of the University of Oregon Medical School.

Early in 1943 the patient began to complain of precordial pain and dyspnea and in June (1943) fluoroscopic examination revealed dilatation of the base of the ascending aorta with marked increase in the pulmonary hilar shadows which extended downward and obscured the outline of the diaphragm.

A roentgenogram of the chest, taken on July 6, 1943, was described as follows: "The cardiac shadow is partially obscured by densities which extend outward from

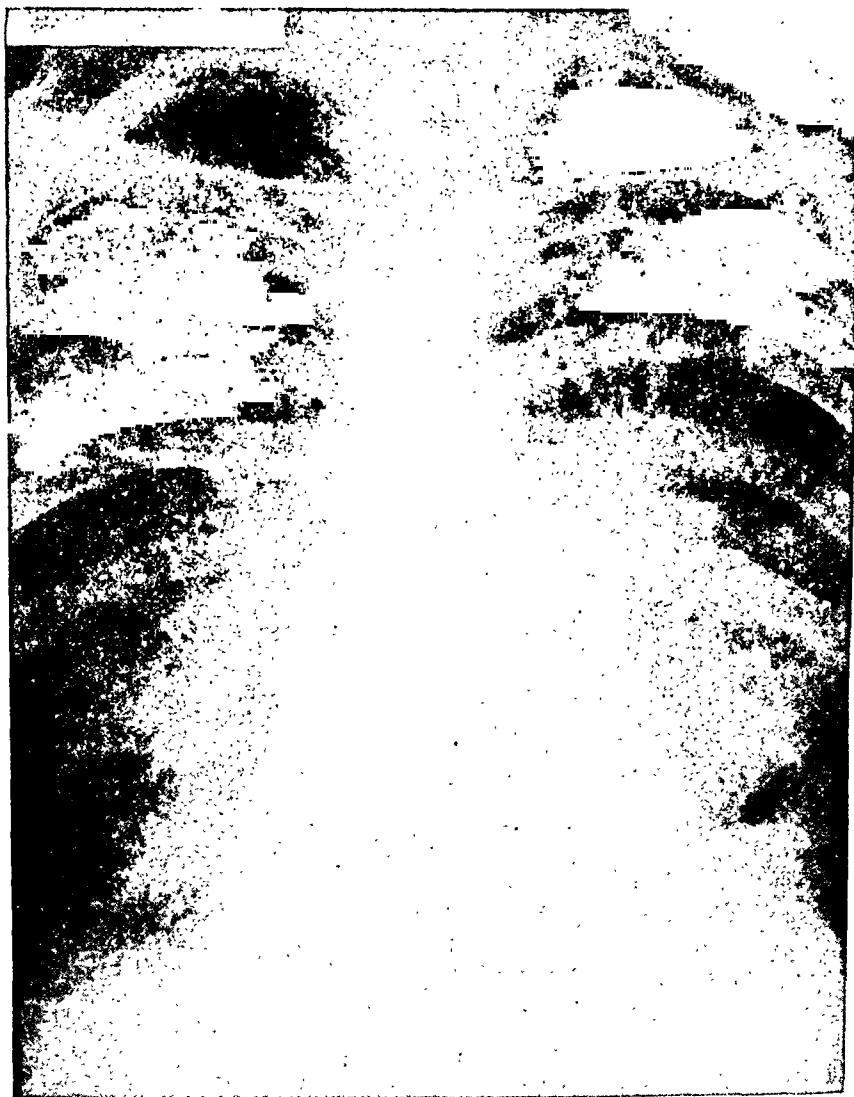


FIG. 1. Roentgenogram of chest taken July 6, 1943, showing enlargement of pulmonary artery shadows at both hilar areas which more or less obscure the outline of the cardiac silhouette. Curved linear calcifications are seen to extend on either side of the eighth to tenth dorsal vertebrae suggesting the presence of an aneurysm of the ascending aorta.

both hilar shadows into the inner two-thirds of the lung fields. Both pulmonary artery shadows appear to be enlarged. These densities in the lung fields extend down to both leaves of the diaphragm and fade out in the outer zones of the chest. Extending to either side of the eighth, ninth, and tenth dorsal vertebrae are two curved linear calcifications, approximately 4 cm. in length. The aortic knob also contains a rim of calcium. It is most likely that the curved linear densities represent an

aneurysm of the descending aorta. The heart shows moderate generalized enlargement."

Fluoroscopically there was seen slight motion in the calcified walls of the aneurysm. The hilar shadows showed exaggerated motion. Both leaves of the diaphragm moved normally.

Another film taken one month later (August 12, 1943) showed some further

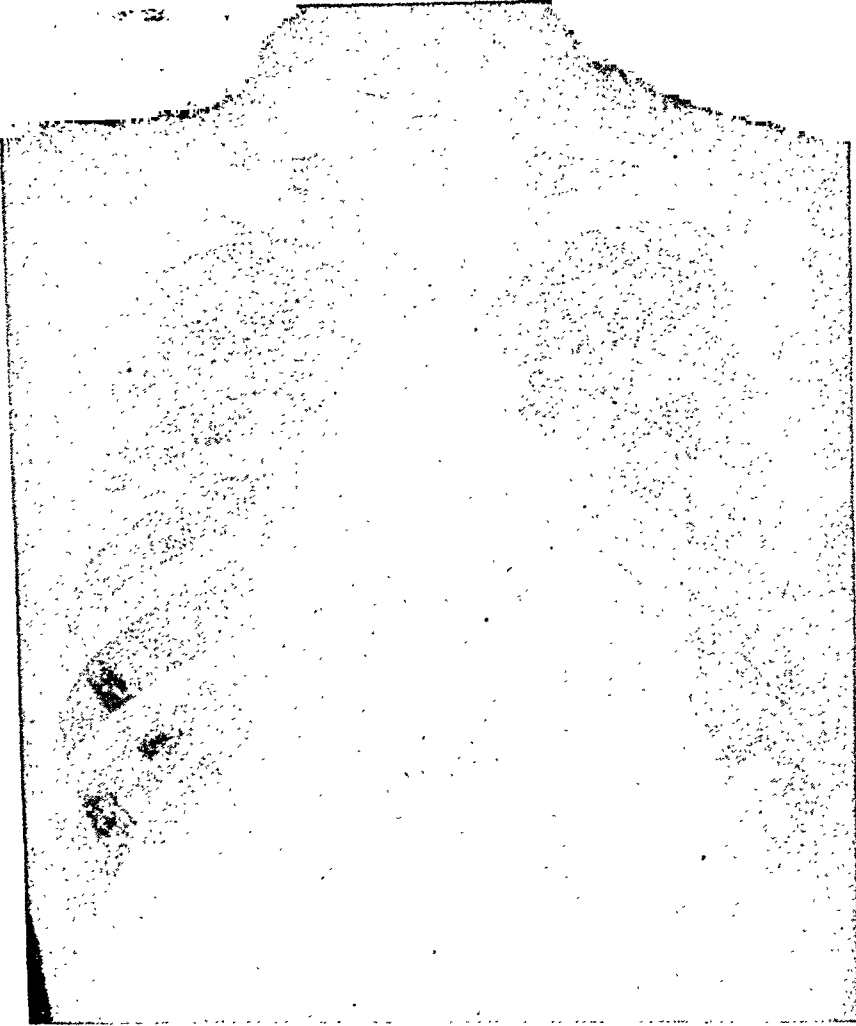


FIG. 2. Roentgenogram of chest taken August 12, 1943, showing more advanced changes in the cardio-pulmonary shadows suggesting the presence of cor pulmonale.

enlargement of the cardiac shadow and a relatively larger increase in the hilar densities.

Electrocardiograms taken on August 16 and October 8, 1943, showed a progressively increasing right axis deviation and right ventricular strain.

The roentgenograms and electrocardiograms indicated the presence of a cor pulmonale.

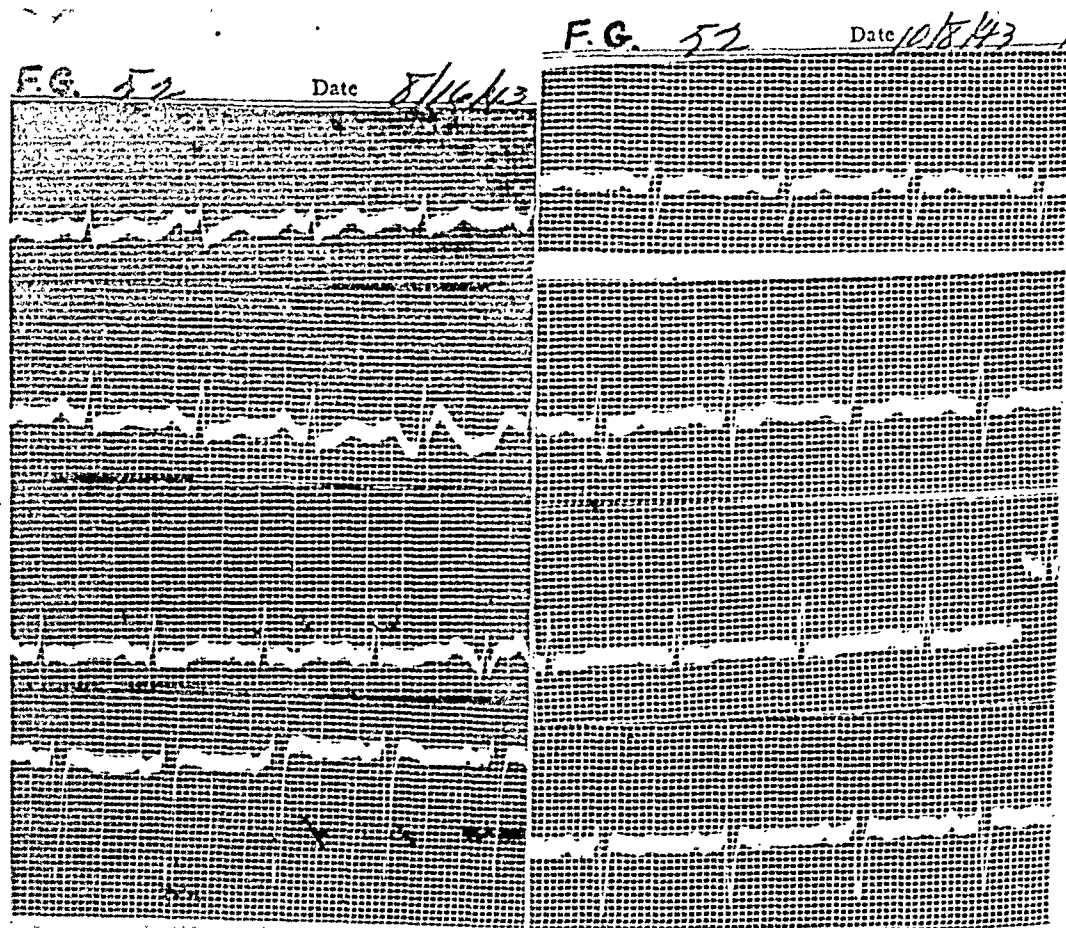
On August 14, 1943, the patient was admitted to the Multnomah Hospital with signs of advanced right-sided heart failure. A loud systolic murmur was heard all over the left second and third intercostal spaces. A short soft aortic diastolic murmur



was heard along the left margin of the sternum. The pulse was of the collapsible or Corrigan type, and the blood pressure was 135 mm. Hg systolic, 35 to 0 mm. diastolic.

Despite the prolonged intensive treatment for syphilis, the blood Kolmer and Kahn reactions remained strongly positive (four plus).

Shortly after admission to the hospital, this case was reviewed at one of the regular weekly clinical conferences, at which time a diagnosis of syphilitic aneurysm of the ascending aorta was established. However, it was further suggested that due



A.

B.

FIG. 3. A. Electrocardiogram taken August 16, 1943, showing right axis deviation and right ventricular strain. B. Electrocardiogram taken October 8, 1943, indicating progressively increasing right axis deviation and right ventricular strain.

to clinical, radiologic and electrocardiographic evidence of cor pulmonale, compression of the pulmonary artery with or without perforation was probably present.

There was little response to the routine measures for congestive heart failure and the progress was continually downward. There was no significant change in the character of the murmur. The signs of congestive heart failure, chiefly right-sided, progressively increased and the patient died on January 16, 1944.

*Autopsy Findings.* The body was that of a well-developed, moderately well-nourished white male who appeared the stated age of 53 years. The external examination revealed moderate edema of the lower extremities, the scrotum, prepuce, and the posterior dependent parts of the body. No appreciable palpebral edema was seen.

The most important visceral changes were found in the ascending aorta, the pulmonary artery and the heart. About 200 c.c. of pale yellow, serous fluid were present in the pericardial sac. The heart was greatly enlarged, having a maximum transverse diameter of 17 cm. The increased size of the heart was due primarily to the right ventricular and arterial dilatation. There was moderate hypertrophy of the right ventricular myocardium. There was mild hypertrophy of the left ventricular myocardium, but this chamber was not appreciably dilated. There was no evidence of recent infarction or of myofibrosis. There was spherical aneurysmal dilatation of



FIG. 4. Sketch illustrating the site of the aortic aneurysm at *A*, the bulge and perforations into the pulmonary artery at *P*, the widening of the pulmonary artery at *PA*, and the ring of fibrin at *FR*.

the ascending aorta. It had a diameter of 7.5 cm. The right border of the aneurysm was only slightly to the right of the usual position of the ascending aorta. The left border of the aneurysm, however, bulged to the left, pressing against and flattening the displaced main pulmonary artery. The circumference of the pulmonary artery was increased proximal to the bulge. There were two closely approximated openings into the pulmonary artery from the aortic aneurysm. The largest perforation measured 1 by 1 cm. and had the shape of a square with rounded corners. The lower border of the perforation was 3 cm. above the aortic valve commissures. Immediately below the larger opening was a smaller one which measured 6 by 3 mm. Its shape resembled

a small buttonhole. The borders of both openings were smooth and covered by intima. In the left lateral wall of the pulmonary artery opposite the perforations in the aortic wall there was a slightly raised ring of reddish, friable tissue, apparently fibrin. The ring was 1 cm. in diameter. There was no destruction of the pulmonary arterial wall.

The wall of the aneurysm of the ascending aorta was very rigid. There was such a marked amount of atherosclerosis with calcium salt deposition that the intima and subintima resembled an irregularly surfaced egg-shell. On the right lateral and anterior surfaces the aortic adventitia was thickened and there were old fibrous adhesions between the parietal pericardium and the aorta. There were irregular, plaque-like elevations of the pulmonary arterial wall above the openings from the aorta. The intima of the pulmonary artery was not roughened. The plaque-like elevations appeared to be due to irregularities in the closely approximated wall of the aortic aneurysm. A similar change was seen in the left border of the superior vena cava, where the aneurysm bulged against it. In the posterior and left lateral borders of the aneurysm the wall was very thin and seemed devoid of media. The media of the anterior and right lateral borders of the ascending aorta, however, was of the usual thickness.

The aortic valve cusps were only slightly altered. The border of the anterior cusp was slightly "rolled" and thickened. The commissure between the anterior and left posterior cusps was separated by a distance of 1 mm. The corpora Arantii and the commissures were in the same plane. The ostia of the coronary arteries also were about in this same plane. The only change in the coronary arteries was a mild atherosclerosis. There was also moderate atherosclerosis of the descending aorta. The mitral, tricuspid, and pulmonary valves were grossly unchanged.

The 800 c.c. of serous fluid in the peritoneal cavity contained some fibrin clots. A mild edema was present in the small bowel mesentery, the perirenal fat, and the mucosa and submucosa of the gastrointestinal tract. Numerous small hemorrhages were seen in the gastric mucosa and submucosa. The rounded anterior-inferior liver border was 7 cm. from the tip of the xiphoid process. The liver was mottled and had a "nutmeg" appearance. The spleen was hyperemic and slightly enlarged. The mobility of the right kidney seemed increased. In its middle portion there was a depressed area of fibrosis and cyst formation. All the cysts were less than 1 cm. in diameter; some contained a colloid-like material.

The diaphragmatic domes were depressed to the level of the sixth and seventh ribs on the right and left sides respectively. The lungs floated in 1,000 c.c. of serous fluid which were present in both pleural cavities. The visceral pleural surfaces were wrinkled and both lungs were partially atelectatic. There was no evidence of pneumonia or pulmonary infarction. All the other structures and viscera not mentioned above (with the exception of the brain, spinal cord and neck organs, which were not examined) were unchanged.

*Anatomic Diagnosis.* Syphilitic aortitis with aneurysm of the ascending aorta and erosions through the pulmonary artery; dilatation of the pulmonary artery; slight separation of an aortic valve commissure; left ventricular hypertrophy; right ventricular hypertrophy and dilatation; chronic passive congestion of the lungs; bilateral hydrothorax; bilateral pulmonary atelectasis; ascites, chronic passive congestion of the liver and spleen; retroperitoneal edema; focal fibrosis of the right kidney.

The microscopic sections confirmed the above anatomical diagnosis. In addition, the aneurysmal wall disclosed old scars of the media with occasional areas of plasma cell and lymphocytic infiltration. In association with the fibrous adventitial thickening and the pericardial adhesions, there were groups of mononuclear leukocytes and thickened arterioles. The lungs revealed the presence of edema fluid and greatly dilated capillaries of the alveolar walls. There were also focal areas of fibrosis in the alveolar walls.

## COMMENT

A study of the cases in the literature including the present observation suggests that compression of the pulmonary artery may be diagnosed when signs of syphilitic aortic aneurysm are associated with evidence of cor pulmonale. Pronounced hypertrophy and dilatation of the right side of the heart were present in all cases examined at autopsy. Clinically, such right-sided preponderance is less readily demonstrable; however, it may be recognized in most instances by (1) the character of venous engorgement which is largely peripheral or systemic, (2) the radiographic evidence of enlargement of the pulmonary artery and conus, and (3) electrocardiographic evidence of right-sided strain (right axis deviation, tall spiked P-waves in second and third leads, and T-wave alterations, especially in third and fourth leads).

When all these signs are present the diagnosis is relatively simple. However, recognition of pulmonary artery involvement becomes much more difficult when radiographic enlargement of the pulmonary conus is obscured by the shadow of the aneurysm and when the electrocardiogram fails to show specific changes. Significant right axis deviation was present in five of the nine cases in which tracings were available. Nevertheless, *when severe right-sided heart failure (systemic venous engorgement) supervenes in a case of syphilitic aortic aneurysm without any other discernible complication to account for the congestive failure, pulmonary artery compression should be suspected.*

In 84 of the 87 reported cases the aneurysm ruptured into the pulmonary artery and established an arterio-arterial communication; in three cases death occurred from cor pulmonale without rupture. The specific clinical sign indicating arterio-arterial communication is the development of a continuous murmur similar in character to that frequently observed in patent ductus Botalli. It is heard best over the pulmonary valve area and is often accompanied by a thrill. This sign was noted in about 40 per cent of the cases in which murmurs were described. However, even in the absence of such a murmur, arterio-arterial communication may be assumed to be present in view of the great frequency with which it was found at autopsy in the reported cases (84 out of 87).

## SUMMARY

1. A case of compression of the pulmonary artery by a syphilitic aneurysm with arterio-arterial communication recognized during life is reported.

2. It is suggested that an antemortem diagnosis may be made more frequently through the recognition of two possible sets of symptoms or signs, one or both of which may be present in a given case:

A. A combination of signs of aortic aneurysm with clinical evidence of cor pulmonale.

B. The presence of a continuous, machinery-type murmur in the pulmonary valve area similar to that characterizing patent ductus Botalli.

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## PAROXYSMAL VENTRICULAR TACHYCARDIA OCCURRING IN THE ABSENCE OF DEMONSTRABLE HEART DISEASE\*

By BERNARD I. LIDMAN, Major, M.C., A.U.S., F.A.C.P., and JAMES M. LYERLY, Captain, M.C., A.U.S.

THIS case report of ventricular tachycardia is presented because of its occurrence in the presence of an apparently normal heart and as an example of the gratifying response to quinidine sulfate therapy.

Ventricular tachycardia<sup>1, 5, 8</sup> is indicative of the existence of serious disease, although in rare instances no cardiac pathologic lesions may be present. Among those factors thought capable of precipitating its onset are: organic heart disease, digitalis intoxication, excessive indulgence in tobacco and alcohol, marked exertion, and overwhelming fatigue.

Ventricular fibrillation<sup>1, 4, 5, 8</sup> has long been regarded as being a terminal state, incompatible with life if effective ventricular action is not restored rapidly. It is rarely encountered clinically, and then usually in moribund patients. High grade auriculoventricular block, acute coronary artery occlusion, chloroform anesthesia, and electrocution have resulted in ventricular fibrillation.<sup>1, 5</sup> In small experimental animals, application of electric shock directly to the heart may cause this irregularity, from which recovery has occurred in some instances. Overdosage with quinidine, digitalis, and epinephrine may give rise to ventricular fibrillation. This is particularly true in the case of epinephrine, when administered in the presence of a damaged, irritable myocardium.

The case to be reported is unusual because ventricular tachycardia and transient ventricular fibrillation occurred in a patient whose heart was apparently normal.

### CASE REPORT

*Present Illness.* This white male patient, 21 years of age, was admitted to this hospital at 5:10 a.m., May 15, 1944, with the complaint of having been awakened from his sleep at 3:30 a.m. by awareness of a very rapid, irregular heart action. At the onset, he noted marked dyspnea and weakness, but stated that he had no precordial pain although his heart did feel "heavy." He had had a light dinner the previous evening, had used no alcohol or tobacco, and had not engaged in exercise preceding this attack.

*Family History.* Non-contributory. One nephew had had one mild attack of rheumatic fever.

\* Received for publication February 7, 1945.

*Past History.* For one month, at the age of nine, the patient had growing pains in both legs. There was no recurrence. At the age of 15 (1938), while playing basketball, he was forced to rest because he experienced the sudden onset of rapid heart action and shortness of breath; the attack lasted three minutes. Two similar episodes occurred later under like circumstances. There was no restriction of activity by his physician. In February, 1943, he contracted pneumonia, type undetermined, and received sulfonamide therapy. During convalescence, two attacks of pharyngitis were treated with sulfonamides. On March 15, 1943, shortly after becoming ambulatory, he experienced a sudden attack of tachycardia, during which he was admitted to a hospital. On admission, the heart rate was approximately 150, and the rhythm totally irregular. An electrocardiogram, after his rhythm had become regular, showed no abnormalities except for a simple tachycardia. No electrocardiogram was taken dur-

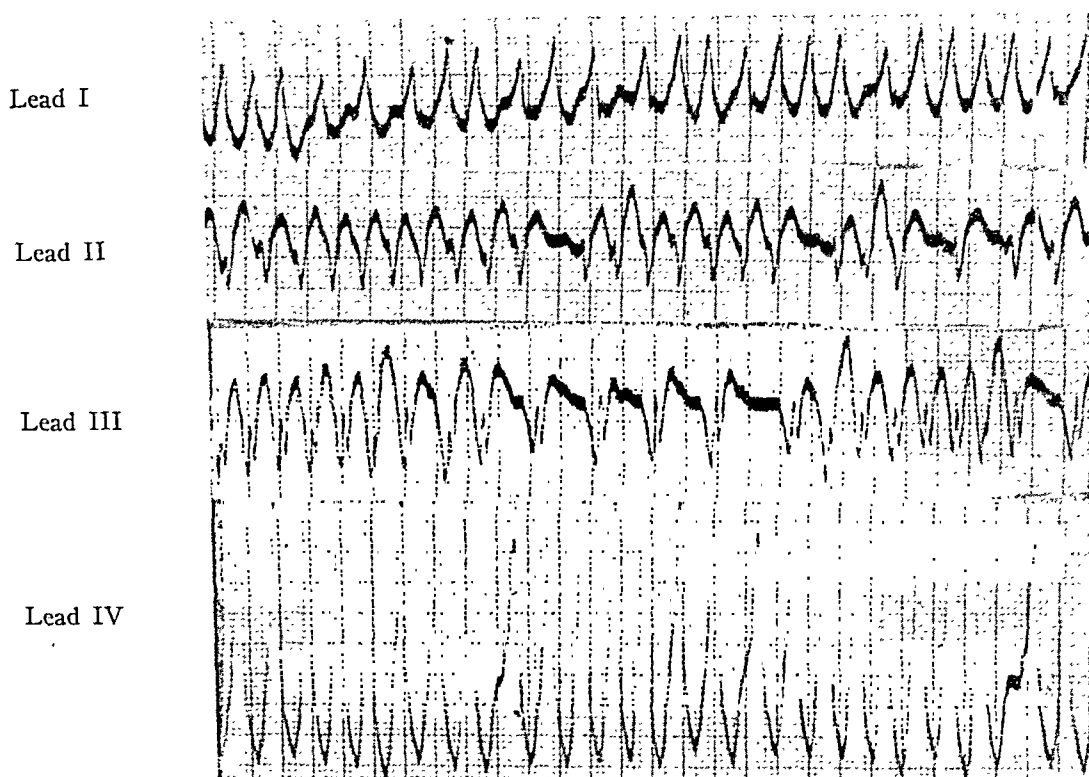


FIG. 1. 6:00 a.m., May 15, 1944.

ing the period of disturbance of cardiac rhythm. He was discharged from the hospital on March 26, 1943, with the diagnosis of paroxysmal auricular fibrillation.

After entering the armed forces, he engaged in the full physical training program without difficulty. He was not aware of any palpitation or tachycardia until the onset of the present illness.

Review of the systems was non-contributory. The patient did not use alcohol, tobacco, or drugs. He did not take any medicine habitually. There was no history of venereal disease.

No evidence of cardiac disease had been discovered during numerous examinations both prior and subsequent to the episode herein described. He had always been an emotionally stable individual.

*Physical Examination.* At the time of admission, 5:10 a.m., the patient had a

slate-gray pallor, but no cyanosis. Marked dyspnea and tachypnea were evident. The pulmonary fields showed no abnormal physical signs. The cervical veins were distended, but there was no hepatomegaly or dependent edema. The heart was not enlarged; the rate was over 200; the rhythm, grossly irregular; there was a pulse deficit of approximately 50. No murmur or friction rub was audible. Blood pressure was 90 mm. Hg systolic and 50 mm. diastolic.

*Course in Hospital.* Morphine sulfate 0.016 gm. was administered immediately, and at 6:00 a.m., an electrocardiogram was made (figure 1). At 7:15 a.m., the cardiac rate could not be counted because of extreme tachycardia; the rhythm was totally irregular. Blood pressure was 96 mm. Hg systolic and 30 mm. diastolic. Because the electrocardiogram was interpreted as showing prefibrillatory ventricular tachy-

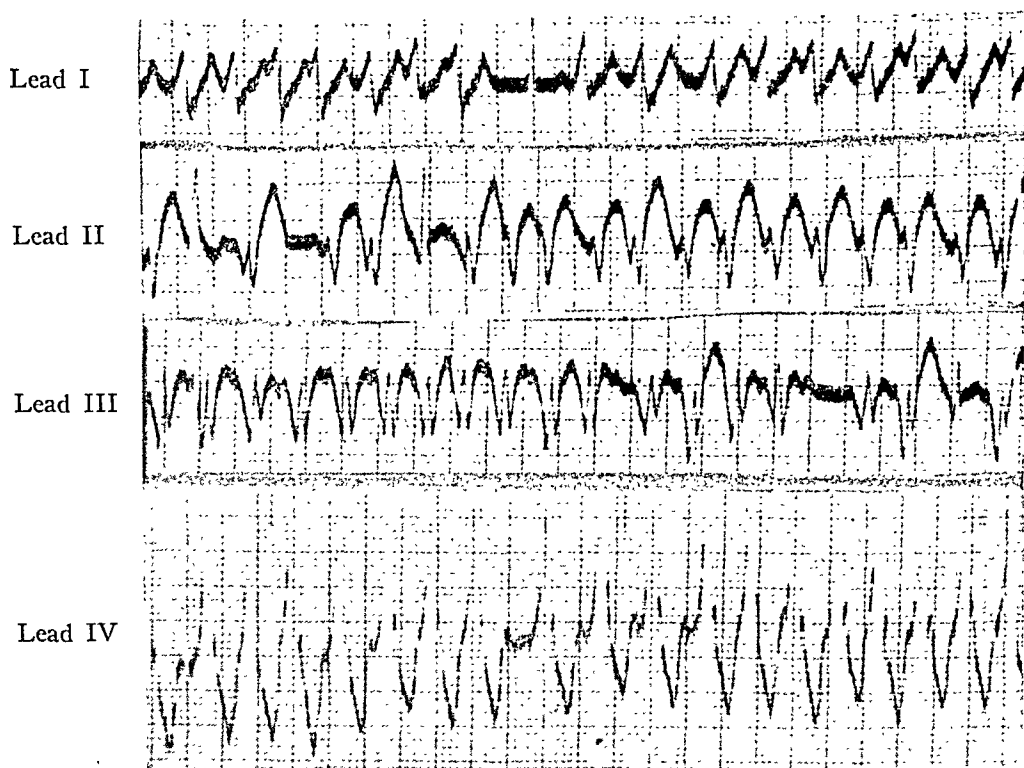


FIG. 2. 10:00 a.m., May 15, 1944.

cardia, or ventricular tachycardia with fibrillation, 1.0 gm. of quinidine sulfate was given at 8:05 a.m. At 9:30, the rate still could not be counted, but periods of regular rhythm became manifest. Blood pressure was 90 mm. Hg systolic and 50 mm. diastolic. At this time, the patient was given an additional 0.3 gm. of quinidine sulfate. An electrocardiographic tracing made at 10:00 a.m. demonstrated persistence of the arrhythmia (figure 2). At 10:45 a.m., an occasional group of heart sounds in regular rhythm was noted, and with the blood pressure at 85 mm. Hg systolic and 40 mm. diastolic, another 0.3 gm. of quinidine was administered.

At 11:00 a.m., 15 minutes after the last dose of quinidine, and following a total dosage of 1.6 gm., normal rhythm suddenly was reestablished, at a rate of 86 beats a minute. Immediately after restoration of regular sinus rhythm (figure 3), the heart sounds were of good quality and intensity, no murmurs were audible, and the blood pressure rose to 104 mm. Hg systolic and 70 mm. diastolic.

The patient was maintained on a dosage of 0.2 gm. of quinidine sulfate every four hours for nine days. On May 24, the dose was reduced to 0.1 gm. three times daily. During this period, the blood pressure had remained at a level of 104–118 mm. systolic, and 70 mm. diastolic. The heart rate averaged 80 to 90. On only one occasion, June 3, 1944, did one examiner note a soft systolic murmur localized to the fourth left interspace. At no other time was a murmur audible.

On June 7, 1944, at 8:00 p.m., the patient had an attack of paroxysmal auricular tachycardia, with a cardiac rate of 170. He was given pantopon 0.02 gm. and quinidine sulfate 0.4 gm.; by the following morning, regular sinus rhythm had again been established.

On June 29, 1944, with the patient in an ambulatory state, he experienced an episode of supraventricular tachycardia, with rate of 260, which responded to opiates and a temporary increase in quinidine dosage.

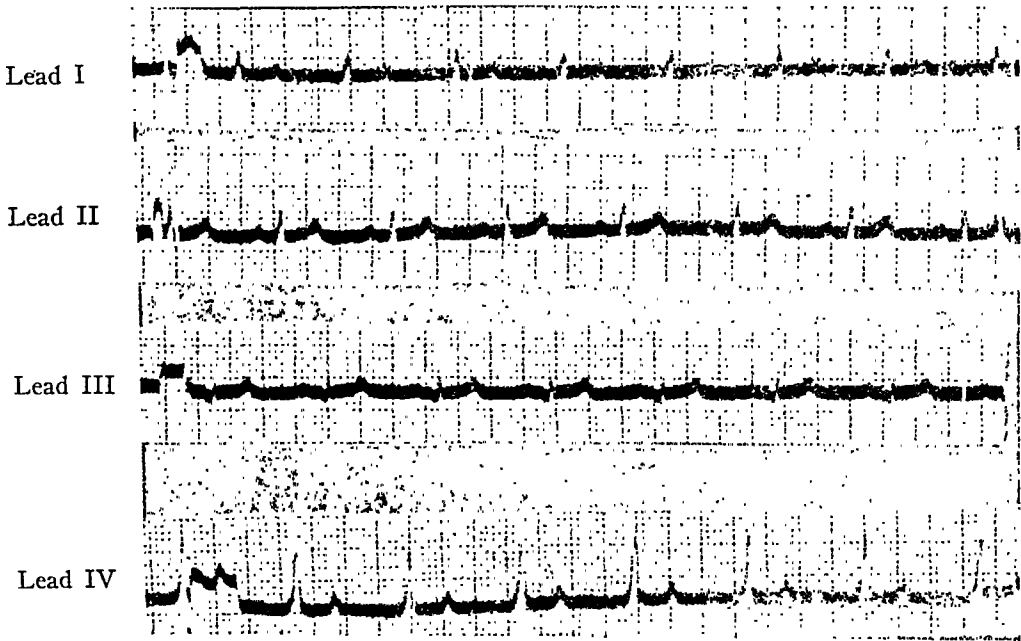


FIG. 3. 11:00 a.m., May 15, 1944.

At no time during the period of hospitalization did this patient have a leukocytosis. Erythrocyte sedimentation rates were at all times within normal limits. Serologic reaction was negative. All blood chemistry studies, including non-protein nitrogen, urea N, sugar, chlorides, cholesterol, calcium, phosphorus, and serum proteins, were normal. Basal metabolic rate was — 15 per cent. Radiographic examination revealed the heart to be normal in size and contour.

This patient was reexamined at frequent intervals, and at no time was evidence of underlying cardiac disease discovered. The last study prior to this report was made on November 11, 1944.

*Electrocardiographic Studies.* Figures 1 and 2: These tracings were made at the height of the paroxysm, and fulfill the criteria for the diagnosis of ventricular tachycardia.<sup>1, 3, 4, 5, 7</sup> The main deflections are ventricular in type, widened, and notched, and occur independently of the superimposed P-waves. The complexes are unidirectional; and vary in rate from 225 to 285 with an average of 260. In figure 1, Lead III, the first six complexes are of one type, and complexes 10 to 14 in this lead



are of another type, with transitional forms between them. It might be said that each series is an arrhythmia arising in a different focus. The rate is much more rapid than that usually seen in paroxysmal ventricular tachycardia. These records might be referred to as a prefibrillatory type of ventricular tachycardia; however, they strongly resemble records of paroxysmal ventricular fibrillation overlying an impure ventricular tachycardia.

Figure 3: This record was made immediately after restoration of normal rhythm. The QRS complexes appear to be of low voltage, but standardizing deflections indicate 0.5 cm. for 1 mv., so that the QRS amplitude is within normal limits. There is no evidence of auriculoventricular block.

Serial electrocardiographic tracings made after this attack indicate no evidence of myocardial damage.

### DISCUSSION

As previously stated, it is generally believed that ventricular tachycardia rarely if ever occurs except as a result of cardiac disease, and is of grave prognostic significance, as it may predispose to ventricular fibrillation.

In the case presented, except for growing pains at the age of nine years, there is nothing which might suggest an antecedent history of cardiac disease. The attacks of palpitation which occurred at the age of 15 were exertional in type, and no evidence of heart disease was discovered at that time. In 1943, a period of arrhythmia occurred during the patient's convalescence from an acute infection. In the present attack, no predisposing factor could be determined; and following the episode of arrhythmia, no evidence of organic cardiac disease could be discovered. Repeated sedimentation rates, leukocyte counts, serial electrocardiograms, and physical examinations did not reveal evidence of coronary artery disease, rheumatic heart disease, thyrotoxicosis, or heart block. There were no manifestations of inflammatory or circulatory change in the myocardium. The patient had undergone several physical examinations for flying qualification and never had the question of heart disease arisen.

Ventricular fibrillation, the most serious of all arrhythmias, is usually considered to be incompatible with life. However, paroxysmal ventricular fibrillation does occur, although usually in patients who have a high-grade auriculoventricular block,<sup>6</sup> and then may be the cause of Stokes-Adams attacks. In such instances, with the ventricular output minimal, cerebral anoxemia results.<sup>2</sup>

Just as some cases of paroxysmal auricular tachycardia and auricular fibrillation occur without demonstrable organic disease, paroxysmal ventricular tachycardia of the prefibrillatory type and ventricular fibrillation may exist as purely functional disturbances with no demonstrable anatomicopathological substratum.<sup>5</sup>

In view of the fact that previous episodes of palpitation were of short duration and ceased spontaneously, with no definitive diagnosis established by clinical or electrocardiographic study, it cannot be assumed those episodes were ventricular tachycardia. Because the attack as described herein was the most severe and of the longest duration experienced by the patient, and because there was no response to morphine sulfate within two hours of its administration, it is conceivable that quinidine sulfate played a distinct, and probably a specific rôle in the reestablishment of normal rhythm within two hours and 40 minutes after the initial dose, and after a total dosage of 1.6 gm.

## SUMMARY

A case of an unusual arrhythmia, consisting in paroxysmal prefibrillatory ventricular tachycardia, with overlying transient ventricular fibrillation, occurring in a young individual, with no demonstrable evidence of heart disease, is presented.

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## ELECTROCARDIOGRAPHIC CHANGES FOLLOWING HEAT STROKE; REPORT OF A CASE \*

By ROBERT BRUCE LOGUE, Major, M.C., F.A.C.P., and JAMES FLETCHER HANSON, Major, M.C., F.A.C.P.

CARDIAC involvement in heat stroke is generally recognized. One frequently finds marked dilatation of the right ventricle with intense pulmonary congestion at autopsy. At other times the ventricles are firmly contracted in systole. Wilson<sup>1</sup> reported subendocardial hemorrhage in the septal region of the left ventricle in four cases. Motta<sup>2</sup> exposed rabbits to wet and dry heat and was able to produce a variety of cardiac conditions, such as sinus tachycardia, nodal rhythm, ventricular extrasystoles, paroxysmal auricular tachycardia, auricular flutter, auricular and ventricular fibrillation, 2 to 1 heart block,  $Q_1$  and T-wave changes and increased auriculoventricular and intraventricular conduction time.

Metz<sup>3</sup> reported three cases with electrocardiographic changes which included bundle branch block in one case, inverted  $T_1$  in one case, and posterior myocardial infarction in one case. The latter changes were probably coincidental. The rarity of reports on electrocardiographic changes in heat stroke prompts the present case report.

## CASE REPORT

A white private, aged 27, was admitted to the Station Hospital on June 3, 1943. He had been playing volley ball on a hot day and several hours later was found in his

\* Received for publication July 26, 1944.

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room in an unconscious state. He was irrational and was giving drill orders. Physical examination showed the patient to be extremely restless and agitated. The skin was hot, dry, and slightly cyanotic. The temperature was recorded as 109° F. The pupils were constricted and did not react. The pulse rate could not be counted accurately, but was thought to be 140 a minute. The blood pressure could not be obtained. The examination of the heart showed it to be of normal size. No murmurs were heard. Laboratory data on admission showed a red blood cell count of 4.3 million. The hemoglobin was 95 per cent (Tallquist). A white blood cell count was 11,700. Urinalysis showed a specific gravity of 1.016, 3 plus albumin, occasional

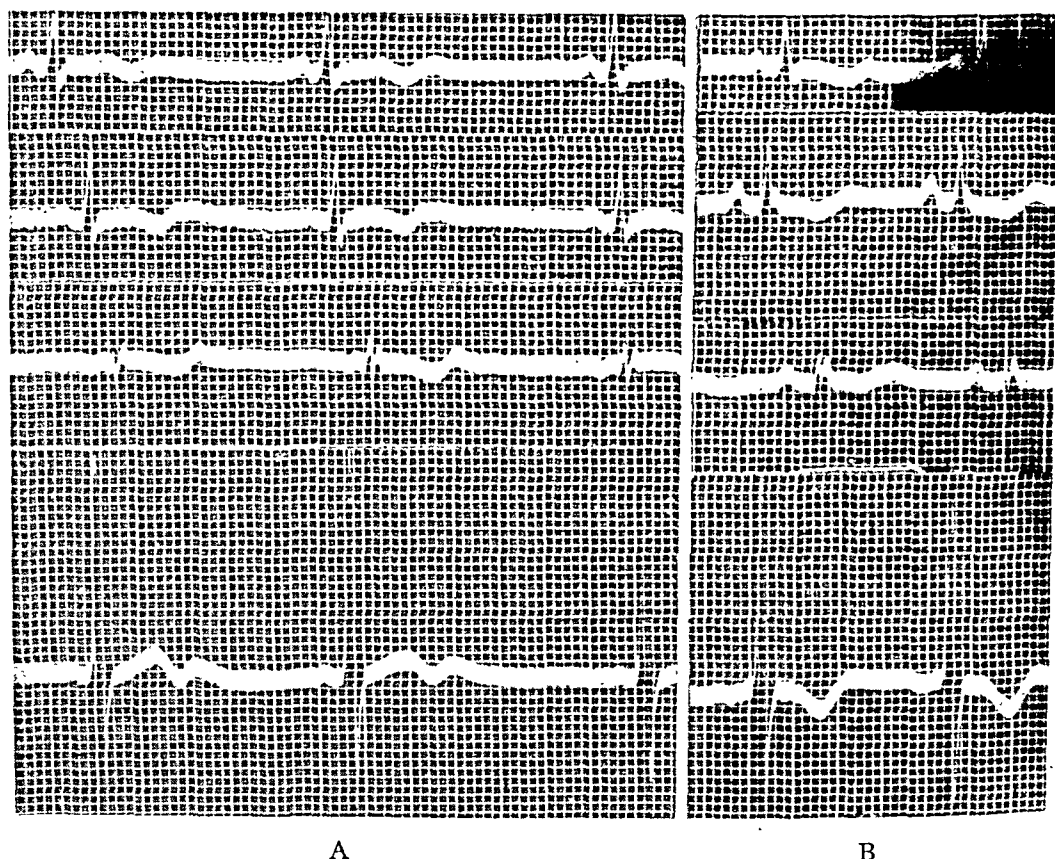


FIG. 1. Electrocardiogram (A) on eleventh and (B) on twenty-first hospital days.

hyaline and granular casts, and 2 to 4 red blood cells and 1 to 2 white blood cells in each high power field.

The patient was sprayed and massaged, and four hours later the temperature had fallen to 105° F. The next morning the temperature was 102.6° F. At this time the patient was incontinent and mentally confused, but could answer questions. The pulse was thought to show an occasional irregularity. He was given 1500 c.c. of plasma and six ampules of digiglusin intramuscularly over a period of 24 hours. On the third hospital day the patient was noted to be jaundiced. The red blood cell count was 4.3 million, and the hemoglobin was 75 per cent. The white blood cell count was 3,900. Other laboratory data at this time revealed a bleeding time of 12 minutes, a clotting time of five minutes, and a platelet count of 91,600. The total protein content of the blood plasma was 6.4 gm., with 4 gm. of albumin and 2.4 gm. of globulin. The

cephalin-cholesterol flocculation test was 3 plus. The icterus index was 57. Subsequently the patient developed ascites, a palpable liver and spleen, and albuminuria, with many red and white blood cells in the urine. The icterus index gradually returned to normal over a period of one month.

On the eleventh hospital day an electrocardiogram showed sinus bradycardia, inversion of the T-waves in all leads, and prominent U-waves (figure 1-A).

On the twelfth hospital day the cephalin cholesterol flocculation test was 2 plus, and on the seventeenth hospital day it was 1 plus.

On the twenty-first hospital day there was deeper inversion of the T-waves in Lead IV (figure 1-B). Two months after the original electrocardiogram, the tracing

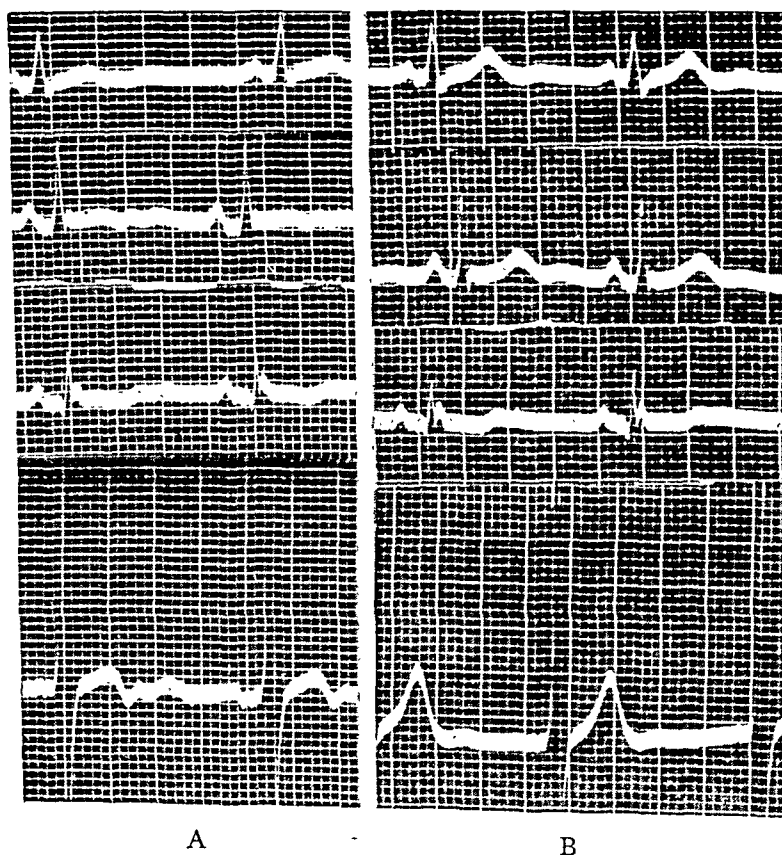


FIG. 2. Electrocardiogram after (A) two months and (B) three months.

showed slight inversion of  $T_1$  and diphasic  $T_2$  and inverted  $T_3$  and  $T_4$  (figure 2-A). Three months after the original electrocardiogram the tracing had returned to normal, but U-waves were still present (figure 2-B).

During convalescence the patient complained of nervousness and a slight tremor of the hands. These had been present for some years but were exaggerated following the heat stroke. An occasional low grade fever, reaching as high as  $99.6^\circ$  was noted.

A psychiatric consultant made a diagnosis of psychoneurosis with anxiety state. An electroencephalogram taken on July 27, 1943 showed "an underlying encephalopathy revealed by almost complete absence of the basic rhythm and a markedly increased fast rhythm." A repeat record taken three months later showed a normal borderline tracing. There was evidence of gradual brain recovery, and a distinct re-

turn towards normal with increase in amplitude and the appearance of the basic rhythm with 10 waves a second; continued intermittent appearance of low amplitude waves of 6 a second, and some increase beyond normal of the fast waves to 20 to 25 a second.

### COMMENT

The presence of jaundice is of some interest and may have been due to direct action on the liver by the hyperpyrexia, to the administration of plasma, or it may have been coincidentally present. The sudden appearance and rapid subsidence suggest that it was a toxic effect of the hyperpyrexia. Jaundice has been reported incident to artificial fever therapy, as well as to natural exposure.<sup>4</sup> The occurrence of anemia, plus evidence of renal damage, might suggest a hemolytic reaction, although ascites is not usually seen in this condition.

The nature of the electrocardiographic changes is somewhat confusing, since the patient had been in profound shock and a digitalis preparation had been administered for 24 hours. Digitalis may cause inversion of the T-waves in all leads; however, the absence of depressed or sagging ST segments, the normal PR interval, and time required for the changes to disappear made this unlikely. Inversion of the T-waves in all leads may be seen following extremely rapid rates,<sup>5</sup> but this was not felt to be a factor in the present case. The pulse rate as recorded on admission was admittedly inaccurate, but was thought to be about 140. Subsequent pulse recordings in the first 24 hours were rapid, but not excessively so.

The changes noted are similar to those seen in pericarditis. The elevation of the ST segments which is usually seen in the early stages of this condition, is not present; however, the first tracing was not taken until the eleventh hospital day. In view of the reports of hemorrhage into the septum, subendocardial hemorrhage, and hemorrhage beneath the pericardium<sup>6</sup> observed at autopsy following sunstroke, it is possible that the changes were perhaps associated with subepicardial hemorrhage or pericardial hemorrhage. Hemorrhagic manifestations are not uncommon in heat stroke, and it is evident that diffuse capillary damage is a not infrequent occurrence. The bradycardia was perhaps a vagal effect of central origin, and is of some interest in view of the electroencephalographic changes suggestive of encephalopathy. The sinus bradycardia disappeared after two months, and a repeat electroencephalogram made one month later showed a return to normal.

### SUMMARY

A case of heat stroke, in which the electrocardiographic changes observed were suggestive of those seen in pericarditis, is reported. The changes were associated with sinus bradycardia and gradually disappeared over a period of two and one-half months.

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## EDITORIAL

### *THE Rh FACTOR*

SINCE the practical significance of the Rh agglutinin and its corresponding agglutinin was shown by Wiener and Peters<sup>1</sup> in 1940, a great deal of intensive study has been devoted to this subject. This has revealed many facts of great theoretical interest and of practical importance. The subject has become so intricate, however, and the diversity in nomenclature so confusing that recent publications are apt to bewilder the average reader who has no first hand acquaintance with this work. The earliest work on this subject was reviewed briefly in these pages.<sup>2</sup> Some of the subsequent developments will be summarized but, for the sake of clarity and simplicity, shorn of much detail. Wiener, Levine, Race, Taylor and their associates have contributed largely to this work.

As a rule, any individual is compatible as a donor if he belongs to the same major blood group as the recipient. In rare instances, however, individuals who had received repeated transfusions of homologous blood eventually developed a severe hemolytic reaction even though in some cases the same donor had been used previously without causing any reaction. A careful study of the blood in three such cases<sup>1</sup> revealed the presence in the recipients' serum of agglutinin which caused clumping of the donor's cells. This was due to the presence of an agglutinable substance in the donor's cells which is different from the agglutinogens A and B which determine the major blood groups. The new agglutinin was designated Rh, because the corresponding agglutinin was identical with one which Landsteiner and Wiener had produced in rabbits by inoculations of blood from rhesus monkeys.

By means of such human sera as well as serum from "immunized" animals they demonstrated that this Rh factor (agglutinin) was present in the red cells of 85 per cent of random white individuals. In the 15 per cent of Rh-negative persons anti-Rh agglutinins ordinarily are not demonstrable. They may appear, however, after sensitization by repeated transfusions of Rh-positive blood. They may also appear, independent of transfusions, in women who are pregnant with an Rh-positive fetus, particularly in cases of erythroblastosis fetalis. Such women may give a hemolytic reaction to the first transfusion of Rh-positive blood. It is believed that fetal red blood cells enter the maternal circulation, presumably through defects in the placenta, and stimulate the development of anti-Rh agglutinin. Conversely, the agglutinin may pass from the maternal into the fetal circulation and

<sup>1</sup> WIENER, A. S., and PETERS, H. R.: Hemolytic reactions following transfusions of blood of homologous group, with 3 cases in which same agglutinin was responsible, *Ann. Int. Med.*, 1940, xiii, 2306-2322.

<sup>2</sup> Editorial: The significance of human atypical isoagglutinins, *Ann. Int. Med.*, 1941, xv, 927-929.

injure the red blood cells, causing the anemia. The antigenic activity of the Rh factor, however, seems to be relatively feeble, since agglutinins appear in only about 2 to 4 per cent of the cases in which they might be expected.

The Rh factor is not a single simple substance. Further study showed that different human anti-Rh agglutinating sera differ qualitatively in their action on different Rh-positive cells. Three specific varieties of anti-Rh agglutinating sera have been described: (1) the standard anti-Rh serum (since designated as anti-Rh<sub>0</sub> agglutinin by Wiener), which agglutinates the red cells of 85 per cent of white individuals; (2) a second type, anti-Rh', which agglutinates the cells of 70 per cent; and (3) a type, anti-Rh'', which agglutinates only 30 per cent. There are about 2 per cent of individuals who are Rh-positive but not revealed by the first type of serum. Sera occur which contain two of these agglutinins, e.g. anti-Rh<sub>0</sub> and anti-Rh', and anti-Rh<sub>0</sub> and anti-Rh''.

Those red cells which are Rh-positive contain agglutinable factors corresponding to these three agglutinins, which Wiener has termed Rh<sub>0</sub>, Rh', and Rh''. These factors occur, either singly or in combination, to form at least five (probably seven) different agglutinogens or antigens. Wiener<sup>3</sup> has designated these as Rh', Rh'', Rh<sub>0</sub>, Rh<sub>1</sub> (= Rh<sub>0</sub>'), and Rh<sub>2</sub> (= Rh<sub>0</sub>''). The British investigators have postulated the existence of two additional antigens, Rh<sub>γ</sub> (= Rh'') and Rh<sub>z</sub> (= Rh<sub>0</sub>''), both very rare, of which only the latter has been demonstrated.

These agglutinogens are inherited as dominant Mendelian characters, through pairs of allelic genes, one from each parent. There are five (possibly seven) such genes corresponding to the agglutinogens listed, designated Rh', etc., and a sixth, *r*h, a recessive character which, when homozygous, determines an Rh-negative individual.

By means of the three varieties of anti-Rh agglutinating sera it is possible to divide all human beings into eight Rh Types or 'groups.' The designations and frequency of these Types in the white population are given by Wiener<sup>3</sup> as follows: Rh<sub>1</sub> Rh<sub>2</sub>, 13 per cent; Rh<sub>1</sub>, 54.5 per cent; Rh<sub>2</sub>, 15 per cent; Rh<sub>0</sub>, 2 per cent; Rh' Rh'', 0.01 per cent; Rh', 1.2 per cent; Rh'', 0.3 per cent; and Rh-negative, 13.5 per cent. The relative frequency of the types varies in other races. In Mongolians Rh-negative individuals are extremely rare.

A study of mothers with infants with erythroblastosis has shown that in about 92 per cent of the cases the mother is Rh-negative, whereas the fetus is Rh-positive, having inherited the Rh factor from the father. In 8 per cent, however, the mother is Rh-positive, and some other type of incompatibility must be concerned. Levine<sup>4</sup> reported finding agglutinins in the serum of such a case, which acted on an agglutinable factor in the fetal

<sup>3</sup> WIENER, A. S.: The Rh blood factors, Jr. Am. Med. Assoc., 1945, cxxvii, 294. (Correspondence.)

<sup>4</sup> LEVINE, P., BURNHAM, L., KATZIN, E. M., and VOGEL, P.: Rôle of iso-immunization in pathogenesis of erythroblastosis fetalis, Am. Jr. Obst. and Gynec., 1941, xlii, 925-937.



red cells which was analogous to but different from the Rh factor. He termed this the Hr factor, because the corresponding anti-Hr agglutinin in its activity was just the reciprocal of the anti-Rh' agglutinin. This serum agglutinated the bloods of 80 per cent of white individuals including all those who are Rh-negative. This observation was confirmed and extended by Race and Taylor<sup>5</sup> who advanced the theory (which is accepted by Wiener) that the 'Hr factor' is determined in the cells (of the fetus) by certain of the Rh factors: viz., rh, Rh<sub>0</sub>, Rh'' and Rh<sub>2</sub>. If these factors are absent from the mother (who must possess other Rh factors, Rh<sub>1</sub> or Rh', since she is "Rh-positive"), she may become sensitized to them just as if she were completely Rh-negative.

The Hr factor seems to be only feebly antigenic, since this relationship has been found in less than 3 per cent of the cases of erythroblastosis. Theoretically an Hr-negative recipient might be sensitized by repeated injections of Hr-positive blood, but no report of such a case has been found. The British investigators postulate the existence of two other Hr factors and anti-Hr agglutinins reciprocal in their action to anti-Rh<sub>0</sub> and anti-Rh'' agglutinin. One case of the latter type has been described.

There is no universally accepted explanation as to why erythroblastosis rarely if ever occurs as a result of incompatibility between mother and fetus with respect to the major isoagglutinogens A and B; e.g., when a mother belongs to Group O, and the fetus to A or B. In a majority of individuals in the latter groups, however, the group substance, A or B, is present not only in the red cells but also in the plasma, the cells of many other tissues and in the secretions. Such cases are called secretors. It has been suggested that the group substance (A or B) which is in the plasma or elsewhere combines with any anti-A or anti-B agglutinin that may pass from the maternal into the fetal circulation and thus prevents its reaching and injuring the red cells. The Rh factor seems to be limited to the red cells and not present in the other tissues or secretions.

As might be expected there are still differences of opinion regarding the explanation of these complicated relationships. Bloods are occasionally encountered which do not fit perfectly into this scheme. The discrepancy may be in the agglutinability of the red cells or in the agglutinative activity of the serum. There is some evidence that other varieties of specific agglutinating serum occur which may define additional Rh Types.<sup>6</sup> There is one discrepancy which warrants brief mention. Although in about 90 per cent of the cases of erythroblastosis the mother is Rh-negative, in a substantial number of the latter the serum shows no anti-Rh agglutinating activity. It was shown independently by Wiener and by Race<sup>7</sup> that if Rh-

<sup>5</sup> RACE, R. R., and TAYLOR, G. L.: Serum that discloses genotype of Rh-positive people, *Nature*, 1943, clii, 300.

RACE, R. R., TAYLOR, G. L., CAPPELL, D. F., and MCFARLANE, M. N.: Recognition of further common Rh genotype in man, *Nature*, 1944, cliii, 52.

<sup>6</sup> LEVINE, P.: On the Hr factor and the Rh genetic theory, *Science*, 1945, cii, 1-4.

<sup>7</sup> RACE, R. R.: Incomplete antibody in human serum, *Nature*, 1944, cliii, 771-772.

positive cells are added to such serum, in many cases the cells lose their agglutinability in other potent anti-Rh serum. Wiener attributed this inhibition of agglutination to "blocking" antibodies, Race to "coating" or "incomplete" antibodies, in the sense that although they combine with the Rh factor in the cells and prevent potent agglutinin from acting later, they are unable to bring about the actual clumping. The demonstration of such specific inhibition of agglutination may probably be regarded as proof that the individual was sensitized.

One may now well ask, what is the practical significance of all this complicated business. As far as the subdivision of the Rh factor into types is concerned, there are as yet few opportunities to utilize this practically. Their determination may be useful for medicolegal purposes, e.g. in excluding paternity, along with a study of the other isoagglutinogens. If the necessary sera are available, and some of them are very rare indeed, in the case of the father of an infant with erythroblastosis it may be possible in certain cases to determine his genotype,<sup>5</sup> and predict whether all or only half of his future children are likely to have the disease. Such matters are only for the specialist.

In certain cases, however, in selecting donors for transfusion it is of great practical importance to know whether the recipient and donor are Rh-positive or negative. For this purpose the usual anti-Rh serum suffices, since only 0.5 to 2 per cent of Rh-positive bloods will be missed. For the average laboratory, there are practical difficulties in finding and preparing suitable sera. The most dependable sera are obtained from mothers of infants with erythroblastosis. Except in large clinics such cases are relatively rare, and in only a part of these cases do the mothers yield serum which has a sufficiently high agglutinin titer to be dependable for diagnostic purposes. Such sera tend to weaken rapidly, both in vitro and in vivo, and may become useless within a few weeks. Furthermore anti-A or anti-B agglutinin must be removed by adding specific A and B substance. This may be prepared from the saliva of secretors. Fortunately for laboratories unable to cope with these difficulties, it is now possible to purchase reliable standard anti-Rh serum which is ready for use.

The tests are best carried out in small test tubes, rather than in hanging drops, and the results observed both macroscopically and microscopically. Incubation should be in the water bath at 37° C., since a large majority of the sera are most active at that temperature. In rare cases, however, agglutination is stronger in the ice box. The technic of performing the tests is not complicated or difficult. At best, however, the agglutinations produced by these sera are usually feeble as compared with those observed in ordinary group determinations, and correspondingly greater care is required to obtain reliable results.

The most practicable way of making this information available to all who need it is probably by establishing special Rh-typing laboratories in connection with state or city Health Departments, as has recently been done

in Baltimore by the Obstetrical and Gynecological Section of the Baltimore City Medical Society.

In summary, tests for the Rh factor should be carried out: (1) on all individuals receiving repeated transfusions; (2) on women pregnant or recently pregnant, regardless of previous transfusions; and (3) on a sufficiently large number of normal individuals to provide a working list of Rh-negative donors available for emergencies. If the prospective recipient is Rh-negative, it is highly advisable to secure an Rh-negative donor. A transfusion, if badly needed, should not ordinarily be withheld on this account, since the chance of a severe reaction is less than 1 in 25. An Rh-negative donor is imperative, however, for a patient who tends to react increasingly to repeated transfusions, and for mothers of infants with erythroblastosis. If an infant with erythroblastosis is to be transfused, the mother should never be used as a donor.<sup>8</sup> Almost anyone else may ordinarily be used provided they are compatible with respect to the major blood groups. It is probably advisable, however, to avoid using as donors those who have themselves received transfusions of blood or injections of plasma.

<sup>8</sup> Washed red cells from the mother may be used.

## REVIEWS

*Recent Advances in Neurology and Neuropsychiatry.* By W. RUSSELL BRAIN, M.A., D.M. (Oxon.), F.R.C.P., and E. B. STRAUSS, M.A., D.M. (Oxon.), F.R.C.P. 363 pages; 21 × 14 cm. 1945. The Blakiston Company, Philadelphia. Price, \$5.00.

This book in its fifth edition needs little more to be said about it than has been said before. In its previous editions it has been considered a good guide to the subject with clear and comprehensive discussions of the various viewpoints. As always there is a full bibliography for each topic for the use of those who want more detailed information. In addition to being full of well selected facts it is well written and easily read. Although the title includes neuropsychiatry the emphasis throughout is almost entirely on neurology and even the few more psychiatrically pointed chapters deal with the subject matter from a neurological rather than a functional viewpoint.

The first part of the book deals with headaches and intracranial disease. The recent work with histamine in the production of headaches and the rationale for the use of ergotamine tartrate in migraine is touched upon. This leads to a discussion of the use and value of various diagnostic methods in cases of suspected intracranial disease. Meningitis in its various forms, with the emphasis on head symptoms, brings in the uses of the newer drugs of the sulpha group and penicillin. What can and cannot be expected of these drugs is well illustrated.

The next section deals with the more nearly neuropsychiatric problems. Electro-encephalography, prefrontal leukotomy and electro-convulsant therapy are given a thorough discussion. The uses and abuses of all three are thoroughly evaluated. The authors feel that electro-encephalography has made great stride but also realize its limitations in diagnosis if used without other diagnostic procedures. They are fair to the enthusiasts about prefrontal leukotomy but feel it is a procedure to be tried only after careful consideration and after efforts to treat in less drastic methods have failed. Head injuries, their diagnosis, prognosis and treatment are discussed in this section also and some of the things that have been helpful in treating them which have been learned through these other procedures. Electroconvulsant therapy is described in great detail and with enthusiasm. The authors feel it is indicated particularly in the affective psychoses, but cite cases where it has been used with some benefit in almost any psychotic or even psychoneurotic condition. The pathology and symptomatology of Alzheimer's and Pick's diseases are described and the differential diagnosis is made to appear much simpler than it actually is in most cases.

After this excursion into neuropsychiatry the book comes back to more purely neurological subjects, the anatomy and functions of the hypothalamus, the neurophysiology of micturition and defecation, the neurotropic viruses and the diseases they cause. These topics are all interestingly discussed and the newer concepts emphasized. There is a good description of much of the research in the physiology and anatomy of the functions of micturition and defecation.

The rest of the book takes up briefly the topics of vitamins and their rôle in neurology and neuropsychiatry, the peripheral nerves, their regeneration and degeneration after injury, the muscular diseases, sciatica and the current enthusiasm for operation in its treatment and an interesting type of shoulder girdle neuritis. In discussing all of these things the newer research and the old concepts are given a fair description with the authors taking a rather conservative attitude but ready to give the new treatment and theories a trial.

Altogether this is a factual, unbiased book covering the field of neurology, and

touching its relationship to neuropsychiatry (more actually in the foreword than in the text), which anyone interested in the field of neurology or psychiatry or, indeed, general medicine will find a convenient reference work for looking up a subject briefly or for finding in it a reference to more detailed work.

R. K. G.

*Case Studies in the Psychopathology of Crime.* By BEN KARPMAN, M.D. 738 pages; 21 × 28 cm. Medical Science Press, Washington, D. C. 1944. Price, \$10.00.

This is the second volume in a series of three, reporting a study on the psychopathology of crime. The first volume was published in 1933 and was reviewed in this journal. The third volume is yet to come off the press. The author is a psychoanalyst, and a Senior Medical Officer at St. Elizabeth's Hospital, Washington, D. C., the Federal hospital for the insane. He has had unlimited opportunity to study psychopathic criminals committed from the Federal Prisons.

In the first volume Karpman presented a detailed study of five cases. In this volume he presents the psychoanalysis of four cases, but without his psychoanalytic interpretation. The material is presented without expurgation and the reader has no difficulty in recognizing the psychological mechanisms involved. In the first volume the cases were studied psychogenetically rather than psychoanalytically. The four cases presented in this volume were charged with sexual crimes and the reader cannot miss the etiological factors underlying this type of misbehavior. The anamnesis is clearly presented and one concludes that if the individuals had been properly handled in childhood, they would not have set off on their careers of crime. There is no doubt that crime prevention begins in infancy and childhood, rather than adulthood.

The tabulation of criminal behavior, conduct in prisons, and drug addiction is well worth reading and is accurate for detail.

This ponderous volume is certainly not for the lay reader, but for the physician interested in social problems, it is an excellent source for case study and may well act as a model for thoroughness and exactness.

J. L. McC.

#### BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*A Synopsis of the Diagnosis of the Surgical Diseases of the Abdomen.* Second Edition. By JOHN A. HARDY, B.Sc., M.D., F.A.C.S. 528 pages; 20 × 13 cm. 1945. C. V. Mosby Company, St. Louis. Price, \$5.00.

*In the Doctor's Office.* By ESTHER JANE PARSONS. 295 pages; 19.5 × 13.5 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, \$2.00.

*Modern Urology for Nurses.* By SHEILA MAUREEN DWYER, R.N., B.S., and GEORGE W. FISH, M.D. With a foreword by Helen Young, R.N. 287 pages; 20.5 × 14 cm. 1945. Lea & Febiger, Philadelphia. Price, \$3.25.

*Prescribing Occupational Therapy.* Second Edition. By WILLIAM RUSH DUNTON, JR., M.D. 151 pages; 22.5 × 14.5 cm. 1945. Charles C. Thomas, Springfield, Illinois. Price, \$2.50.

*War Neuroses.* By ROY R. GRINKER, Lt. Col., M.C., and JOHN P. SPIEGEL, Major, M.C., Army Air Forces. 145 pages; 23.5 × 16 cm. 1945. The Blakiston Company, Philadelphia. Price, \$2.75.

*Penicillin in the Treatment of Infections.* By CHESTER S. KEEFER, B.S., M.S., M.D., ScD. (Hon.), and DONALD G. ANDERSON, A.B., M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., ScD. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work. 51 pages; 24 × 16 cm. 1945. Oxford University Press, New York. Price, \$1.50.

*Hematology for Students and Practitioners.* By WILLIS M. FOWLER, A.B., M.D., with a chapter by ELMER L. DEGOWIN, A.B., M.D. 499 pages; 24 × 16.5 cm. 1945. Paul B. Hoeber, Inc., New York. Price, \$8.00.

*Guía de Trabajos Practicos (Serie Aromática).* 225 pages; 27.5 × 19 cm. 1945. Universidad Nacional de Tucuman. Facultad de Farmacia y Bioquímica. Catedra de Química Orgánica Cíclica.—Publicación No. 372. Tucuman, República Argentina.

# COLLEGE NEWS NOTES

## A.C.P. MEMBERS IN THE ARMED FORCES

### *Additions*

At the time of the release of this news item, the following 52 additional Fellows and Associates of the American College of Physicians, recently elected, have been added to the list of members on active military duty during World War II, making a grand total of 1,980:

Leonard Max Asher, Los Angeles, Calif. (Major, MC, AUS)  
Oscar Auerbach, Staten Island, N. Y. (Lieutenant, MC, USNR)  
Noyes Latham Avery, Jr., Ann Arbor, Mich. (Major, MC, AUS)  
Arthur Dwight Baldwin, Wellesley, Mass. (Captain, MC, AUS)  
Malcolm Lynn Barnes, Louisville, Ky. (Captain, MC, AUS)  
William Edwin Barnett, Logansport, Ind. (Major, MC, AUS)  
Ward Wright Briggs, Wilmington, Del. (Lieutenant Commander, MC, USNR)  
Norman Quintus Brill, New York, N. Y. (Lieutenant Colonel, MC, AUS)  
Heinrich Georg Brugsch, Boston, Mass. (Lieutenant, MC, AUS)  
Thomas Edison Clark, Columbus, Ohio (Lieutenant, MC, USNR)  
Wilfrid Joseph Comeau, Bangor, Maine (Lieutenant Colonel, MC, AUS)  
William Dean Coventry, Duluth, Minn. (Major, MC, AUS)  
Arthur Charles Darrow, St. Louis, Mo. (Major, MC, AUS)  
Nicholas John Di Gregorio, Brooklyn, N. Y. (Major, MC, AUS)  
Henry Dunlop Ecker, (Passed Assistant Surgeon, USPHS)  
Robert William Elliott, St. Louis, Mo. (Major, MC, AUS)  
Roberto Francisco Escamillo, San Francisco, Calif. (Major, MC, AUS)  
Walter Goldfarb, New York, N. Y. (Major, MC, AUS)  
Robert Philip Harvey, Denver, Colo. (Major, MC, AUS)  
Thomas Gideon Hobbs, Chicago, Ill. (Major, MC, AUS)  
Milton E. Hubbard, Los Angeles, Calif. (Lieutenant Colonel, MC, AUS)  
Lewis Edward January, Iowa City, Iowa (Major, MC, AUS)  
William Allen Jeffers, Philadelphia, Pa. (Major, MC, AUS)  
Milosh Kasich, Weehawken, N. J. (Lieutenant Colonel, MC, AUS)  
Robert Willis Kimbro, Cleburne, Tex. (Captain, MC, AUS)  
Gerald Klatskin, New Haven, Conn. (Major, MC, AUS)  
J. Elliot Levi, Baltimore, Md. (Captain, MC, AUS)  
Isaiah Edward Libin, New York, N. Y. (Captain, MC, AUS)  
Joseph Francis Linsman (Colonel, MC, USA)  
Mischa J. Lustok, Milwaukee, Wis. (Lieutenant Colonel, MC, AUS)  
Harold Aloysius Lyons (Lieutenant Commander, MC, USN)  
Lumir Martin Mares, Wenatchee, Wash. (Major, MC, AUS)  
Harold Henry Marquis, San Francisco, Calif. (Major, MC, AUS)  
Theodore H. Mendell, Philadelphia, Pa. (Lieutenant Colonel, MC, AUS)  
Louis Merves, Philadelphia, Pa. (Captain, MC, AUS)  
Richard Marion Nay, Rochester, Minn. (Lieutenant, MC, AUS)  
Leslie Staebler Pierce, Greensburg, Pa. (Major, MC, AUS)  
Leon Rosove, Santa Monica, Calif. (Lieutenant Commander, MC, USNR)  
John Jerome Rupp, Santa Barbara, Calif. (Commander, MC, USNR)  
Robert Bruce Rutherford, Peoria, Ill. (Colonel, MC, AUS)  
John Paul Sauvageot, Akron, Ohio (Captain, MC, AUS)  
Ralph Kenneth Shields, Bethlehem, Pa. (Captain, MC, AUS)

Norman Richard Shulack, Brooklyn, N. Y. (Major, MC, AUS)  
 Leslie Benjamin Smith, Phoenix, Ariz. (Lieutenant Colonel, MC, AUS)  
 Spicknall, Charles Gassaway (Surgeon, USPHS)  
 Irwin Daniel Stein, Mt. Vernon, N. Y. (Captain, MC, AUS)  
 Robert Harold Talkov, Boston, Mass. (Captain, MC, AUS)  
 Leonard Tarr, New York, N. Y. (Major, MC, AUS)  
 Paul Luke White, Austin, Tex. (Major, MC, AUS)  
 Donald Eugene Wood, Indianapolis, Ind. (Major, MC, AUS)  
 Donovan George Wright (Lieutenant Commander, MC, USN)  
 Thomas Ziskin, Minneapolis, Minn. (Major, MC, AUS)

The following members of the College have recently been separated from active duty:

James P. Baker, Richmond, Va. (Lt. Col., MC, AUS)  
 L. Minor Blackford, Atlanta, Ga. (Major, MC, AUS)  
 Oscar Blitz, New Orleans, La. (Col., MC, AUS), (Associate)  
 Joseph G. Bohorfoush, Madison, Wis. (Major, MC, AUS)  
 William J. Bondurant, Jr., San Antonio, Tex. (Lt. Col., MC, AUS)  
 George A. Boylston, Wilmette, Ill. (Major, MC, AUS), (Associate)  
 J. Russell Brink, Grand Rapids, Mich. (Lt. Comdr., MC, USNR), (Associate)  
 Daniel Noyes Brown, Westport, Conn. (Capt., MC, AUS)  
 Morton Goodwin Brown, Boston, Mass. (Lt. Col., MC, AUS), (Associate)  
 Benjamin Burbank, Brooklyn, N. Y. (Major, MC, AUS)  
 Hildahl Ingbert Burtness, Santa Barbara, Calif. (Comdr., MC, USNR)  
 Roy Edwin Butler, New Orleans, La. (Senior Surgeon, USPHS)  
 Asher Spafford Chapman, Oyster Bay, N. Y. (Capt., MC, AUS), (Associate)  
 David Hale Clement, Buffalo, N. Y. (Capt., MC, AUS)  
 Stuart R. Combs, Terre Haute, Ind. (Capt., MC, AUS), (Associate)  
 Joseph Russell Cook, Huntington, W. Va. (Major, MC, AUS), (Associate)  
 Crispin Cooke, New York, N. Y. (Capt., MC, AUS), (Associate)  
 Dolph Lange Curb, Houston, Tex. (Lt. Col., MC, AUS)  
 Hal Davis, Roanoke, Va. (Capt., MC, AUS), (Associate)  
 Norman Walter Drey, St. Louis, Mo. (Lt. Col., MC, AUS), (Associate)  
 J. Richard Durham, Wilmington, Del. (Major, MC, AUS)  
 Eli Eichelberger, York, Pa. (Capt., MC, AUS), (Associate)  
 David E. Engle, Elmhurst, Ill. (Major, MC, AUS), (Associate)  
 Irving Ershler, Binghamton, N. Y. (Major, MC, AUS)  
 William Dustin Evans, Los Angeles, Calif. (Major, MC, AUS), (Associate)  
 Edwin G. Faber, Tyler, Tex. (Col., MC, AUS)  
 Isidore Albert Feder, Brooklyn, N. Y. (Lt. Col., MC, AUS)  
 James Owen Finney, Gadsden, Ala. (Major, MC, AUS)  
 Dan W. Fisher, Lansing, Mich. (Lt. Col., MC, AUS), (Associate)  
 Arthur Conwell Fortney, Fargo, N. D. (Major, MC, AUS)  
 Carl H. Fortune, Lexington, Ky. (Lt. Col., MC, AUS)  
 Dale G. Friend, Boston, Mass. (Col., MC, AUS)  
 Victor K. Funk, Oak Terrace, Minn. (Comdr., MC, USNR)  
 Clark C. Goss, Seattle, Wash. (Capt., MC, USNR)  
 George C. Griffith, Philadelphia, Pa. (Lt. Comdr., MC, USNR)  
 Lawrence J. Halpin, Cedar Rapids, Iowa (Major, AUS), (Associate)  
 Samuel Hantman, Cleveland, Ohio (Major, MC, AUS), (Associate)  
 Carl A. Hartung, Chattanooga, Tenn. (Major, MC, AUS)  
 Theodore S. Heineken, Bloomfield, N. J. (Major, MC, AUS), (Associate)  
 Ferdinand C. Helwig, Kansas City, Mo. (Lt. Col., MC, AUS)



Joe E. Holoubek, New Orleans, La. (Major, MC, AUS), (Associate)  
Ralph C. Hoyt, Reading, Pa. (Major, MC, AUS)  
Robert R. Janjigian, Forty Fort, Pa. (Lt. Col., MC, AUS)  
William Karl Keller, Louisville, Ky. (Lt. Comdr., MC, USNR)  
LeMoyné Copeland Kelly, New York, N. Y. (Comdr., MC, USNR)  
Roy E. Kinsey, Peekskill, N. Y. (Major, MC, AUS), (Associate)  
Jack D. Kirshbaum, Chicago, Ill. (Lt. Col., MC, AUS)  
Jacob Joseph Kirshner, Philadelphia, Pa. (Lt. Col., MC, AUS), (Associate)  
Andrew J. V. Klein, East Orange, N. J. (Capt., MC, AUS)  
James Edward Knighton, Jr., Shreveport, La. (Lt. Col., MC, AUS)  
Rudolph A. Kocher, Carmel, Calif. (Lt. Col., MC, AUS), (Associate)  
Alfred L. Kruger, Jersey City, N. J. (Capt., MC, AUS), (Associate)  
Edward R. H. Kurz, Brooklyn, N. Y. (Major, MC, AUS)  
Louis H. Landay, Pittsburgh, Pa. (Lt. Col., MC, AUS)  
William A. Lange, Brooklyn, N. Y. (Lt. Col., MC, AUS)  
Sidney Leibowitz, New York, N. Y. (Lt. Col., MC, AUS), (Associate)  
Joseph Levy, New Rochelle, N. Y. (Capt., MC, AUS), (Associate)  
Max August Lindauer, Philadelphia, Pa. (Capt., MC, AUS), (Associate)  
Louis S. Lipschutz, Eloise, Mich. (Lt. Col., MC, AUS), (Associate)  
Victor Wesley Logan, New York, N. Y. (Capt., MC, USNR)  
Hugh MacDonald, Glenview, Ill. (Lt. Col., MC, AUS), (Associate)  
Dean W. Marquis, East Orange, N. J. (Comdr., MC, USNR)  
George Elmer Martin, Pittsburgh, Pa. (Lt. Col., MC, AUS), (Associate)  
George Graydon Martin, Buffalo, N. Y. (Comdr., MC, USNR)  
Edward Matzger, San Francisco, Calif. (Lt. Comdr., MC, USNR), (Associate)  
Charles K. Maytum, Rochester, Minn. (Col., MC, AUS)  
Jesse McCall, Newton, N. J. (Lt. Col., MC, AUS)  
Ernest G. McEwen, Evanston, Ill. (Major, MC, AUS)  
John McDowell McKinney, New York, N. Y. (Lt. Comdr., MC, USNR)  
John R. E. Morgan, Toronto, Ont. (Lt. Col., RCAMC)  
Samuel Nesbitt, New Haven, Conn. (Lt., MC, USNR)  
George Francis O'Brien, Chicago, Ill. (Lt. Col., MC, AUS)  
Sidney G. Page, Jr., Richmond, Va. (Major, MC, AUS), (Associate)  
Harold W. Palmer, Wichita, Kans. (Major, MC, AUS)  
Elmus D. Peasley, Raleigh, N. C. (Major, MC, AUS), (Associate)  
Paul August Petree, Harrisburg, Pa. (Lt. Col., MC, AUS), (Associate)  
Morton Morris Pinckney, Richmond, Va. (Major, MC, AUS), (Associate)  
Norman Plummer, New York, N. Y. (Major, MC, AUS)  
L. Paul Ralph, Grand Rapids, Mich. (Comdr., MC, USNR), (Associate)  
William A. Read, Cleveland, Ohio (Lt. Col., MC, AUS), (Associate)  
W. Grady Reddick, Dallas, Tex. (Lt. Comdr., MC, USNR)  
Samuel T. R. Revell, Jr., Baltimore, Md. (Capt., MC, AUS), (Associate)  
Harold F. Robertson, Philadelphia, Pa. (Lt. Col., MC, AUS)  
Max Harry Rosenblum, Steubenville, Ohio (Major, MC, AUS), (Associate)  
Owen Royce, Jr., Oklahoma City, Okla. (Major, MC, AUS), (Associate)  
John W. Skinner, Kirkland, Wash. (Capt., MC, USNR)  
Joseph Sklaver, Waterbury, Conn. (Capt., MC, AUS), (Associate)  
Carter Smith, Atlanta, Ga. (Lt. Col., MC, AUS)  
Walter M. Solomon, Cleveland, Ohio (Lt. Col., MC, AUS)  
James Ward Sours, Peoria, Ill. (Lt. Comdr., MC, USNR)  
Alfred Stengel, Jr., Philadelphia, Pa. (Capt., MC, AUS)  
Franz H. Stewart, Miami, Fla. (Lt. Comdr., MC, USNR)  
Dar Delos Stofer, Monterey, Calif. (Capt., MC, USNR)  
James M. Strang, Pittsburgh, Pa. (Lt. Col., MC, AUS)

Paul Richard Swanson, Chattanooga, Tenn. (Capt., MC, AUS), (Associate)  
 James Shirley Sweeney, Dallas, Tex. (Col., MC, AUS)  
 Charles F. Sweigert, San Francisco, Calif. (Lt. Col., MC, AUS), (Associate)  
 James M. Suter, Bristol, Va. (Major, MC, AUS), (Associate)  
 William A. Thornhill, Jr., Charleston, W. Va. (Lt. Comdr., MC, USNR), (Associate)  
 R. Carmichael Tilghman, Baltimore, Md. (Lt. Col., MC, AUS)  
 J. Russell Twiss, New York, N. Y. (Capt., MC, USNR)  
 Gilman R. Tyler, Richmond, Va. (Major, MC, AUS), (Associate)  
 William Clifford Vance, Richmond, Ind. (Capt., MC, AUS), (Associate)  
 Arie C. van Ravenswaay, Boonville, Mo. (Lt. Col., MC, AUS), (Associate)  
 Aloysius Vass, Springfield, Ill. (Capt., MC, AUS)  
 John Orren Vaughn, Santa Monica, Calif. (Comdr., MC, USNR), (Associate)  
 Joseph James Wallace, Washington, D. C. (Major, MC, AUS), (Associate)  
 Arthur Brittan Walter, Saint John, N. B., Can. (Col., RCAMC)  
 Joseph O. Weilbaecher, Jr., New Orleans, La. (Lt. Col., MC, AUS)  
 Thomas J. White, Jersey City, N. J. (Lt. Col., MC, AUS)  
 Hugh Grigsby Whitehead, Jr., Baltimore, Md. (Comdr., MC, USNR)  
 M. Richard Whitehill, Norfolk, Va. (Major, MC, AUS), (Associate)  
 Russell D. Williams, Monterey, Calif. (Major, MC, AUS), (Associate)  
 Sidney E. Wolpaw, Cleveland, Ohio (Major, MC, AUS)

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#### A.C.P. GOVERNORS RETURN FROM MILITARY SERVICE

During the period of the war several members of the Board of Governors of the College have served on active military duty. During their absence Acting Governors were appointed who served meritoriously. With the end of the war the following Governors have now returned and have resumed their active work, relieving the Acting Governors:

Dr. Edward L. Bortz, Philadelphia, Governor for Eastern Pennsylvania, relieving Dr. Thomas M. McMillan, Philadelphia, Acting Governor.

Dr. Douglas Donald, Detroit, Governor for Michigan relieving Dr. Patrick L. Ledwidge, Detroit, Acting Governor.

Dr. Charles E. Watts, Seattle, Governor for Washington, relieving Dr. Edwin G. Bannick, Seattle, Acting Governor.

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#### 27TH ANNUAL SESSION OF THE COLLEGE, PHILADELPHIA, PA., MAY 13-17, 1946

As announced in the December issue of this journal, the 27th Annual Session of The American College of Physicians will be held in Philadelphia, Pa., May 13-17, inclusive, 1946, under the general chairmanship of Dr. George Morris Piersol, 36th and Spruce Streets, Philadelphia 4, Pa. Dr. Piersol is organizing all local arrangements, the program of Morning Clinics, Panel Discussions and entertainment features. Working with him are the following chairmen of local committees: Dr. Edward L. Bortz, Entertainment Committee; Dr. Harrison F. Flippin, Committee on Transportation; Dr. Thomas Fitz-Hugh, Committee on Clinics; Mrs. William D. Stroud, Committee on Ladies' Entertainment.

The President of the College, Dr. Ernest E. Irons, 122 S. Michigan Avenue, Chicago 3, Illinois, is organizing the program of Morning Lectures and Afternoon Scientific Sessions. Many of the speakers and subjects have already been decided upon, but additional titles may be submitted directly to Dr. Irons.

The Executive Secretary, Mr. E. R. Loveland, is responsible for all business arrangements, and for the Technical Exhibit. Some three thousand rooms have been reserved in advance at Philadelphia hotels. The Benjamin Franklin Hotel, 9th and Chestnut Streets, will be general hotel headquarters for Officers, Regents and

Governors, and for such additional members as can be accommodated. A list of hotels and their rates will be published shortly. The Municipal Auditorium, 34th Street below Spruce, will be the headquarters for the Morning Lectures, Panel Discussions, Afternoon Scientific Sessions, Committee Meetings and the Technical Exhibit. It is anticipated that the finest and largest Technical Exhibit ever conducted by the College will be arranged. The Technical Exhibit is conducted on a high plane; all exhibits irrelevant to the practice of internal medicine and its allied specialties will be eliminated. Exhibitors and exhibits will be selected with particular care from an Invitation List already prepared.

Perhaps the greatest feature of the Meeting will be the Victory Convocation on Wednesday evening, in the Grand Ballroom of the Benjamin Franklin Hotel, where Fellowships will be awarded to all physicians who have qualified for Fellowship since the outbreak of the War. An impressive ceremony has been organized, and will be under Dr. Reginald Fitz, Marshal of the College.

#### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows have become Life Members since the publication of the last issue of this journal. They are listed in the order of subscription. The Life Membership fee is deposited in the permanent Endowment Fund of the College, and each Life Member becomes an active Fellow so long as he lives. The Life Membership fees may properly be deducted on Federal income tax returns. This means there is considerable saving on subscriptions to Life Memberships during the period when Federal taxes are high.

Dr. Seymour Harry Silvers, Brooklyn, N. Y.  
 Dr. Samuel Nesbitt, Arlington, Va.  
 Dr. Elmer Edward Glenn, Springfield, Mo.  
 Dr. Wilton Ross Glenney, Pottsville, Pa.  
 Dr. David Wendel Carter, Jr., Dallas, Texas  
 Dr. Irving Gray, Brooklyn, N. Y.  
 Dr. James Francis Slowey, Cleveland, Ohio

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

M. G. Berry, Major, (MC), AUS, Associate, San Francisco, Calif.—1 reprint.  
 Dr. Carlos F. Cardenas y Pupo, F.A.C.P., Havana, Cuba—5 reprints.  
 Samuel Hantman, Major, (MC), AUS, Associate, Greensboro, N. C.—1 reprint.  
 Dr. Benjamin Kaufman, Associate, Brooklyn, N. Y.—1 reprint.  
 Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—3 reprints.  
 Milton Mendlowitz, Captain, (MC), AUS, Associate, San Francisco, Calif.—1 reprint.  
 Dr. Leslie M. Smith, F.A.C.P., El Paso, Tex.—2 reprints.  
 Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio—1 reprint.  
 J. S. Sweeney, Colonel, (MC), AUS, F.A.C.P., Dallas, Tex.—1 reprint.

At the Thirteenth Annual Assembly of The Omaha Mid-West Clinical Society, October 22-26, 1945, twenty-seven Fellows and one Associate of the College appeared on the scientific program or on committees. Of this number, the following were distinguished guests from other states:

Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y., "Peptic Ulcer—A Modern Concept of a Psychosomatic Disease," "Inflammatory Diseases of the Small Intestine,"

"Clinic—Diseases of the Colon"; Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, "The Purpuric States," "The Splenic Dyscrasias: Differential Diagnosis and Treatment," "Clinic—Differential Diagnosis and Therapeutic Rationale in Anemic States," "Round Table—Anemias Which Do not Respond to Orthodox Therapy"; Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Ill., "Newer Developments in the Surgical Treatment of Gastro-duodenal Ulcer," "Surgery of the Pancreas," "Clinic—Duodenal, Gastric and Gastro-jejunal Ulcers," "Round Table—Surgery of the Gall-bladder"; Major Thomas Jan Dry, (MC), AUS, F.A.C.P., Camp Carson, Colo., "Thermal Injuries Occurring under Conditions of Combat," "Scientific Exhibit—Trench Foot and Frost Bite"; Dr. Robert H. Felix, F.A.C.P., Washington, D. C., "Maladjustment in the Returning Veteran—Comments on Etiology and Symptomatology," "Mental Public Health: A Blue Print," "Clinic—Adjustment Problems in Returning Veterans"; Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, "Respiratory Emergencies in the Infant and Child," "Differential Diagnosis of Meningeal Irritations," "Clinic—Children with Neurologic Organic Lesions," "Round Table—Treatment of Contagious Diseases."

#### THE AMERICAN COLLEGE OF PHYSICIANS REGIONAL MEETING FOR NORTH CAROLINA

A Regional Meeting of the College was held at Durham, N. C., November 30, 1945, under the Governorship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, and a committee consisting of Dr. J. P. Rousseau, F.A.C.P., Chairman, Winston-Salem, Dr. E. R. Hedgpeth, F.A.C.P., Chapel Hill, Dr. E. S. Orgain, F.A.C.P., Durham, Dr. F. R. Taylor, F.A.C.P., High Point. The Scientific Program, conducted at Duke Hospital, was as follows:

1. The Nutritional State of the Civilian Population of Southern Germany.  
JULIAN M. RUFFIN, M.D., F.A.C.P., Durham.
2. Blood Coagulation and Modern Clinical Applications.  
JOHN H. FERGUSON, M.D., F.A.C.P., Chapel Hill.
3. The Surgical Treatment of Hypertension.  
KEITH S. GRIMSON, M.D., (by invitation).
4. Subacute Bacterial Endocarditis.  
ROBERT L. McMILLAN, M.D., (associate), Winston-Salem.
5. The Management of Congestive Heart Failure.  
WILLIAM T. RAINEY, M.D., F.A.C.P., Fayetteville.

A Dinner Meeting and Evening Session were held at the Hope Valley Country Club, at which Dr. Whitaker presided. The speaker of the evening was Dr. Frederic M. Hanes, F.A.C.P., Professor of Medicine, Duke University School of Medicine, the subject being "Ameboid Movement of Cancer Cells as a Factor in Metastasis."

A large proportion of Fellows and Associates of the College from the State of North Carolina were in attendance, and in addition there were numerous guests. The entire meeting was declared an outstanding success.

The 1946 Regional Meeting for North Carolina will be held at the Bowman Gray School of Medicine at Winston-Salem, and Dr. E. L. Persons, F.A.C.P., Durham, will be the Chairman of the Program Committee.

#### ACADEMY-INTERNATIONAL OF MEDICINE AND DENTISTRY SEEKS MEDICAL REPRINTS FOR THE DEVASTATED MEDICAL LIBRARIES OF MANILA

In connection with its campaign to help rebuild the medical libraries of Manila which were destroyed during the Japanese occupation, the Academy-International of Medicine requests that medical authors contribute eight or ten reprints of each of their articles which have been published since 1941. They may be sent at the regular

parcel post rate of sixteen cents for the first pound and eleven cents for each additional pound, care of A. B. M. Sison, M.D., Philippine General Hospital, Manila, P. I.

Dr. William W. Cadbury, F.A.C.P., has left the United States to return to Lingnan University at Canton, China. Prior to the war, Dr. Cadbury was Professor of Internal Medicine there and Superintendent of the Canton Hospital.

The Medical Society of the State of Pennsylvania will hold its 96th Annual Session at the Bellevue-Stratford Hotel, Philadelphia, October 7-10, 1946, according to announcement by its Secretary-Treasurer, Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh.

According to a recent announcement, Tulane University of Louisiana School of Medicine, New Orleans, has been given a bequest of \$1,075,000 from Miss Sarah Henderson for the endowment of the chair of tropical medicine and for the improvement and expansion of the department.

Dr. Pascal F. Lucchesi (Associate) has recently been released as a Lieutenant Colonel from an assignment in Uruguay as Chief of a Health and Sanitation Mission for the Commission of Inter-American Affairs and has resumed his duties as Superintendent and Medical Director of the Philadelphia Hospital for Contagious Diseases.

Under the Presidency of Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Virginia, the American Academy of Allergy held its second Annual Meeting at Chicago, December 10-11.

#### MAJOR GENERAL GEORGE F. LULL ACCEPTS APPOINTMENT WITH AMERICAN MEDICAL ASSOCIATION

Major General George F. Lull, (MC), USA, F.A.C.P., Deputy Surgeon General of the United States Army, has accepted an appointment as Assistant Secretary of the American Medical Association, and has already assumed his duties in Chicago. It was recently announced that Dr. Olin West, after a great many years of service, will retire to the status of Secretary Emeritus later in the year, and General Lull will then assume the full duties as Secretary.

General Lull was awarded the Distinguished Service Medal for "exceptionally meritorious conduct in the performance of outstanding services in the Office of The Surgeon General from June 1940 to August 1945." First commissioned into the Army Medical Reserve as a First Lieutenant in 1912, General Lull had reached the rank of temporary Lieutenant Colonel by 1918, though he later reverted to the rank of Major until the confirmation of his rank as Lieutenant Colonel in 1933. In 1939 he was promoted to Colonel, in 1943 to Brigadier General, and later in 1943 to his present rank. He served in France with the AEF as Commanding Officer of Base Hospital No. 35, and, previous to World War I, in the Canal Zone. He served in various positions at Walter Reed General Hospital, including Chief of Laboratory Service, Director of Laboratories and Professor of Bacteriology, Director of the Occupational Therapy Department, and Instructor at the Army Medical School. In addition to these duties, he has served as Assistant to the Eighth Corps Area Surgeon, Medical Advisor of the Governor General of the Philippines, and as Director of Military Personnel and Chief of the Statistical Division in the Office of the Surgeon General.

The citation: "In his capacity as Chief of the Personnel Service he was responsible for developing plans to augment the various officers' corps and the enlisted and civilian personnel of the Medical Department during the nation's first total mobilization of medical manpower. As Deputy Surgeon General, he was largely responsible

for establishing policies and directing studies which resulted in many outstanding medical achievements such as the advancement in preventive health measures, the remarkably low incidence of disease, and the low mortality from both disease and battle wounds. General Lull's skillful discharge of difficult duties and his devotion to the mission of the Medical Department contributed in important degree to the success of the Army's unprecedented medical program."

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Dr. Harold Innman Goslin, F.A.C.P., has accepted the medical directorship of the Wabash Valley Sanitarium at Lafayette, Ind. He began his duties during November.

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Dr. Theodore Rothman (Associate), Los Angeles, Calif., addressed the Los Angeles Society of Neurology and Psychiatry, November 21, 1945, on "Recent Trends in Electroencephalography."

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Dr. Willard C. Rappleye, F.A.C.P., President of the Josiah Macy, Jr. Foundation, New York City, has announced that more than five million copies of over four hundred leading medical and scientific articles have been published by the Foundation's War Reprint Service during the last three years for medical officers of the Armed Forces of the United States, and in so far as possible, Canada, England, New Zealand, Australia, the Union of Socialist Soviet Republics and China. The Reprint Service will now be discontinued because of plans for demobilization of the Armed Forces.

The Reprint Service has been an effort to bring new and important developments in the science and practice of medicine to medical officers who were largely cut off from the sources of medical information during the war. The Committee on Pathology of the National Research Council and of the National Committee for Mental Hygiene actively coöperated in the selection of these articles. The distribution of the reprints was worked out in coöperation with the Surgeons General of the Army and Navy and the Air Surgeon.

In addition to the articles reproduced from journals, the Foundation published for the Air Surgeon, five original monographs, prepared by medical officers of the Army Air Forces, dealing with personality disturbances occurring in combat zones. Over ninety-five thousand copies of these monographs were distributed as official documents of the Office of the Air Surgeon. Eight additional monographs and nine reviews of medical literature on subjects of military interest have been prepared, and seventy thousand copies distributed. Since August 1944, a News Letter for the Rheumatic Fever and Streptococcus Control Program of the Army Air Forces has been published monthly for the Air Surgeon, and over one thousand copies each month were mailed to interested medical officers, military hospitals and medical school libraries. Through the coöperation of the Interdepartmental Committee on Cultural and Scientific Coöperation of the Department of State, sixty thousand reprints have been distributed to medical teachers and investigators in forty-eight foreign countries. The Office of War Information requested permission to circulate the Foundation's reprints among more than thirty of their foreign Outposts, and has reduplicated selected articles for their distribution to medical leaders abroad.

The Foundation expended more than \$225,000 in financing the War Reprint Service.

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Dr. Lester M. Morrison, F.A.C.P., has removed from Philadelphia to Los Angeles, where he has entered the practice of internal medicine at 1911 Wilshire Boulevard.

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Dr. Hyman I. Goldstein (Associate) has been appointed Professor of the History of Medicine at the Essex College of Medicine and Surgery, Newark, N. J.

Dr. Guy G. Lunsford, F.A.C.P., Atlanta, has been appointed Deputy Director of the Georgia Department of Public Health. Dr. Lunsford is a native Georgian, and received his medical education at the University of Georgia and Vanderbilt School of Public Health. He is widely known throughout Georgia, and has been director of the division of local health organizations since 1934, and prior thereto was health officer in Crisp and Jenkins counties.

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#### NEW YORK UNIVERSITY COLLEGE OF MEDICINE ANNOUNCES PLANS FOR A NEW MEDICAL CENTER

New York University has announced plans for construction of a \$27,500,000 Medical Center on the East Side, of which its share will cost \$15,000,000. The project will be known as the New York University-Bellevue Medical Center and Chancellor Harry Woodburn Chase has indicated construction of the University's section would begin in a year or two. The City will spend \$12,500,000 to rebuild its present Bellevue Hospital area, which will adjoin the University's new buildings along First Avenue. The combined project will cover the nine city blocks between 25th and 34th Streets, First Avenue to East River Drive.

The University section of the project will include a new College of Medicine building, a University Clinic, and 480-bed University Hospital, a 279-room Hall of Residence for medical students, a 500-seat auditorium, and an Institute of Forensic Medicine, the latter the first of its kind in the world.

Where Bellevue Hospital devotes most of its services to the very poor, the University project will concentrate on benefits to persons of moderate means. In the hospital, stress will be placed on single rooms, because the tendency is in that direction. But partitions will be removable if there is unexpected demand for ward service.

There will be six institutions housed in New York University structures. One H-shaped building to cost \$8,500,000 will be 19 stories high and contain the clinic on the bottom floors, the College of Medicine above that, and superimposed on them both will be a 14-floor hospital. The Hall of Residence, to provide sleeping quarters for 270 students now living in rooming houses in the Bellevue area, will cost \$750,000.

The Institute of Forensic Medicine will be built by the City on land to be provided by New York University. University faculty members will staff it. It will be the first such institution in the world, and its purpose will be to train a new type of medical examiner with a view to replacing the old coroner system in the field of criminal investigation.

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#### BUREAU OF MEDICINE AND SURGERY ANNOUNCES PROGRAM FOR TRAINING OF SPECIALISTS

Establishment of a long-term program for training of specialists, involving the designation of nine large naval hospitals as special centers of instruction, is announced by Vice Admiral Ross T. McIntire, U.S.N., F.A.C.P., Chief of the Bureau of Medicine and Surgery.

Intended to fulfill more adequately the medical and surgical needs of an expanded peacetime Navy, the program will make available to medical officers a complete term of specialization training comparable to the best obtainable in civil life. All of the recognized specialties will be taught, including anesthesiology, dermatology and syphilology, internal medicine, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedic surgery, otolaryngology, pathology, pediatrics, plastic surgery, psychiatry and neurology, radiology, surgery and urology.

The nine postgraduate teaching centers will be set up at the following naval hospitals: Chelsea, Massachusetts; St. Albans, New York; Philadelphia, Pennsylvania;

Bethesda, Maryland; Great Lakes, Illinois; San Diego, Long Beach and Oakland, California, and Seattle, Washington.

The board of honorary consultants to the Navy Medical Department of the Navy, composed of ranking civilian members of the profession, have actively coöperated in formulation of plans and will assist in their development. The consultants are: Dr. Donald C. Balfour, director of the Mayo Foundation and Clinic, Rochester, Minnesota; Dr. Richard B. Cattell, Chief of the Surgical Section, Lahey Clinic, Boston, Massachusetts; Dr. Edwin J. Cohn, Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts; Dr. Frank P. Corrigan, American Ambassador to Venezuela; Dr. Walter E. Dandy, Professor of Neurosurgery, Johns Hopkins University Hospital, Baltimore, Maryland; Dr. Frank H. Lahey, Director of the Lahey Clinic, Boston, Massachusetts; Dr. Oswald S. Lowsley, Director of the Department of Urology, James Buchanan Brady Foundation, New York, New York; Dr. James E. Paullin, F.A.C.P., Professor of Clinical Medicine, Emory University, Atlanta, Georgia; Dr. W. Calhoun Stirling, Urologist, Washington, D. C.; Dr. Edward A. Strecker, F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Dr. Meyer Wiener, Professor of Ophthalmology, Washington University, St. Louis, Missouri.

Instructors will include not only the regular staffs of the nine special training centers but also members of the naval Reserve Medical Corps who are outstanding in their various fields of medicine and surgery. Duties of the latter, as volunteers, will include consultations in problem cases and organization of the curricula. Headquarters of the program will be in the Bureau of Medicine and Surgery, and a central advisory committee will be created.

Present plans, which are flexible, call for a definite period of training for the young doctor who enters the Navy upon his graduation from medical school. This period would cover one year's internship, one or more years of residency training, two years of sea or foreign shore duty and, finally, a definite period of intensive work in this country in that field of medicine which the officer has chosen and which has been approved by the central advisory group.

Chief advantage of the program, from the individual doctor's point of view, is that it gives him an opportunity to become a specialist without the financial, assignment and other complications which attend the same effort in civil life. The training will not be given to those medical officers who do not wish to specialize or who demonstrate that they are better fitted for general practice.

Internships and residency training will continue to be given at all naval hospitals which are properly accredited, with the more advanced teaching offered at the nine specialization centers. Augmenting the latter will be the postgraduate facilities of a number of civilian teaching institutions, to be announced later.

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#### MISSISSIPPI VALLEY MEDICAL SOCIETY 1946 ESSAY CONTEST

The Mississippi Valley Medical Society is resuming its annual Essay Contest in 1946, and offers a cash prize of one hundred dollars, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best.

Contestants must be members of the American Medical Association and residents of the United States. The winner will be invited to present his contribution before the next Annual Meeting of the Society, to be held at St. Louis, Mo., September 25-27, 1946. The Society reserves the exclusive right to first publish the essay in its official journal. All contributions shall not exceed five thousand words, shall be typewritten in English in manuscript form, and shall be submitted in five copies not later than



May 1, 1946, to Dr. Harold Swanberg, F.A.C.P., Secretary of the Society, 209 W. C. U. Bldg., Quincy, Ill.

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#### PEDIATRIC ANTIQUES ON TOUR

The Collection of Pediatric Antiques, illustrated in the pages of a catalogue just issued, has evolved into one of considerable historical importance, depicting as it does the progression of infants' feeding vessels from the Greece of twenty-five centuries ago down to the present. This Collection was started as a personal hobby of the late E. Mead Johnson, Jr., and it has been steadily growing in size and scope, and is of increasing interest for teaching purposes via the historical route. The destruction of original sources caused by the War tends to add to the value of these objects. The Collection is now available to colleges, hospitals, museums, libraries and other institutions of learning. Application for its use should be sent to the curator, Mead Johnson & Company, Evansville 21, Ind.

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Dr. Dar Delos Stofer, F.A.C.P., has retired as a Captain in the U. S. Naval Reserve, and on December 1, 1945, established private practice at 412 Professional Bldg., Monterey, Calif. Before the War Dr. Stofer was located in Kansas City, Mo.

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#### AMERICAN UNIVERSITY OF BEIRUT IN LEBANON TO CONSTRUCT MEDICAL CENTER

Plans for the construction of a Medical Center at the American University of Beirut, Lebanon, at an estimated cost of \$2,500,000, have been announced by Albert W. Staub, American Director of the Near East College Association, Inc. The University's Board of Trustees has approved this project. The Medical Center will increase the bed capacity of the present hospital by more than 250 per cent, make possible the training of 25 per cent more medical students and treble the size of the Nursing School. Mr. Staub predicted that when the Center is in operation, American medicine will come into the foreground in the Near East.

The Medical Center will provide accommodations for guest research fellows in tropical medicine. Conditions in the Near East are suitable for research in malaria, typhoid fever, dysenteries and typhus, and for the investigation of nutritional diseases in children. As a teaching hospital, the building will contain classrooms in conjunction with clinical work, administrative offices, living quarters for internes, staff suites, rooms for the nursing staff and guest rooms.

The American University of Beirut, one of the eight colleges affiliated with the Near East College Association, was founded in 1866 with a charter from the State of New York. Its Medical School opened a year later. The University is the largest American educational institution outside the United States.

"The Medical Center will enhance American prestige and build up friendship for the United States," Mr. Staub said. "Evidence of the prestige already attained by the American University of Beirut Hospital is the large percentage of its patients who come from countries as far distant as Iraq, Iran and Egypt. It has served members of royal families of several surrounding countries, as well as Lebanese and Syrian ministers who often are alumni of the University."

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Brigadier General William C. Menninger, F.A.C.P., Director of Neuropsychiatry Consultants Division, has been on a tour of inspection of Medical Department installations in the Pacific, including stops at Honolulu, Guam, Shanghai, Chungking, and Tokyo.

A.C.P. POSTGRADUATE PROGRAM FOR 1946  
 At the present writing, plans for our Postgraduate Program for 1946 are about to crystallize. Directors have authorized courses in the following subjects listed:

<i>Subject</i>	<i>Location</i>	<i>Dates</i>	<i>Director</i>	<i>Institution</i>	<i>Capacity</i>
Allergy	Boston, Massachusetts	Mar. 4-9 Apr. 8-13 May 1 wk.	Dr. F. M. Rackemann	Massachusetts General Hospital	6 only 6 only 6 only
Allergy	New York, New York	Nov. 4-16	Dr. Robert A. Cooke	Roosevelt Hospital	30-75
Arthritis	New York, New York	Apr. 15-20	Dr. Ralph H. Boots	Presbyterian Hospital	10-20
Cardiology	Philadelphia, Pa.	May 6-11	Dr. W. G. Leaman, Jr.	Philadelphia General Hospital, and Woman's Medical College	75-100
Chemotherapy	St. Louis, Missouri	Oct. or Nov. 1 wk.	Dr. W. Barry Wood, Jr.	Washington University, and Barnes Hospital	10-20
Chest Diseases	Ann Arbor, Michigan	May 6-11	Dr. John Alexander	University of Michigan	25-75
Gastroenterology	Philadelphia, Pa.	Apr. 29- May 4	Dr. Henry L. Bockus	Graduate Hospital, and Philadelphia General Hospital	—
General Medicine	Atlanta, Georgia	Apr. 22-27	Dr. James Paullin	Emory University	—
General Medicine	Galveston, Texas	Mar. or Apr. 1 or 2 wks.	Dr. Charles T. Stone	University of Texas	—
General Medicine	Philadelphia, Pa.	Mar. 18-23	Dr. Hobart Reimann	Jefferson Hospital	75-100
Hematology	Columbus, Ohio	Oct. 21-26	Dr. Charles A. Doan	Ohio State University	35-75
Internal Medicine	Boston, Massachusetts	Apr. 1-19	Dr. J. H. Means	Massachusetts General Hospital	60-80
Neurology and Psychiatry	Madison, Wisconsin	Nov. 10-16	Dr. Hans H. Reese	University of Wisconsin, and Wisconsin State General Hospital	—

It will be noted that, in a number of these proposed courses, the definite date or dates and maximum and minimum registration have not yet been determined. The fees for all courses will be \$20 per week to members of the College; \$40 per week for non-members; no charge to medical officers on active duty.

A detailed bulletin of the spring courses is in press and will promptly be mailed, together with a registration form, to every member of the College and to non-members who have requested this information.

The postgraduate bulletin of autumn courses will be published in the early summer.

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#### COURSE IN INTERNAL MEDICINE

A general course in the principles and practice of Internal Medicine will be given at the Massachusetts General Hospital in Boston, Massachusetts from April 1 to 19, inclusive, under the Directorship of Dr. J. H. Means, F.A.C.P., who is Jackson Professor of Clinical Medicine at the Harvard Medical School and Chief of Medical Service of the Massachusetts General Hospital.

This proposed course will stress the fundamentals of Internal Medicine and will be limited to a maximum of eighty (80) registrants.

Various members of the Harvard Medical School faculty, who are serving in other Boston hospitals and institutions, will be invited to participate in the presentation of this course.

Registration will begin on or after January 1, 1946.

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#### COURSES IN GENERAL MEDICINE

An intensive postgraduate course in *General and Internal Medicine* will be given in Philadelphia, Pa. at the Jefferson Hospital, from March 18 to 23, inclusive, under the Directorship of Dr. Hobart Reimann, F.A.C.P., who is Professor of Medicine of the Jefferson Medical College and Chief of the Medical Service of the Jefferson Hospital.

This course will deal with the recent advances in Internal Medicine and should be of particular value to returning veteran medical officers.

Registration will be limited to one hundred (100) applicants, and will begin on or after January 1, 1946.

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A course in *General Medicine*, under the Directorship of Dr. James E. Paullin, F.A.C.P., in coöperation with Dr. Eugene A. Stead, who is Professor of Medicine at Emory University, will be given in Atlanta, Georgia from April 22 to 27, inclusive.

The institutions and hospitals listed for the course are: Emory University Medical School in conjunction with the Piedmont, Grady, Emory University and Georgia Baptist Hospitals.

Registration will be limited to a maximum of twenty-five (25) men, and it is expected that a complete outline of the course will be available shortly after January 1, 1946.

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#### COURSE IN CARDIOLOGY

A course in Cardiology will be given in Philadelphia, Pa. by a composite faculty, under the Directorship of Dr. William G. Leaman, Jr., F.A.C.P., who is Professor of Medicine of the Woman's Medical College of Pennsylvania.

Sessions will be held during the daytime at the Philadelphia General Hospital. In the evening, an interesting and rather unusual program, devoted to the basic sciences and their relation to cardiology, will be given by the members of the pre-clinical faculty of the Woman's Medical College in Philadelphia. Recent advances in cardiac anatomy, physiology, pharmacology and pathology in their relation to cardiac

problems will be presented. This program promises information valuable to the general internist as well as to the cardiologist.

Registration will be limited to one hundred (100) applicants, beginning on or after January 1, 1946.

Incidentally, this course directly precedes the annual session of the College, to be held in Philadelphia from May 13 to 17, inclusive.

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#### INFORMATION FOR THE VETERAN MEDICAL OFFICER

During the past two months the office of the Educational Director of the College has been in touch with our Regents and Governors, as well as with the Deans and the Professors of Medicine at teaching centers throughout the country, requesting practical information concerning assistantships, residencies, teaching positions and research assignments available to veteran medical officers who are members of the College and who have recently been returned to inactive duty status or will shortly be released from military service.

Nearly all the larger hospitals and medical schools have expanded their residency and teaching facilities to accommodate their own returning veterans insofar as possible. The demand for specialty training far exceeds the supply of immediately available facilities. As a result, many institutions already have a waiting list of their own graduates and a large backlog of applications from non-graduates who are desirous of further training in the field of Internal Medicine.

As the plan of demobilization of medical officers progresses, the present situation will become more acute, and those who are considering further graduate training in hospital residencies should take definite steps immediately to secure their desired appointments in advance.

It is believed that the best procedure will be for the veteran to contact the medical school from which he graduated and the hospital or other institution where he had served his internship and/or residency prior to his entrance into the armed forces. A well qualified internist should be able to establish himself in a large city in the practice of Internal Medicine without encountering too many obstacles. Smaller towns offer many opportunities of moderate promise, while in the rural areas there is a dearth of well trained clinicians.

Many State and County Medical Societies are performing yeoman work in organizing local placement aid for their former members about to return from active military duty. The American Medical Association has compiled a general overall view of the situation throughout the country. More specific information can be obtained by writing directly to the Bureau of Information of the American Medical Association, or the State and County Medical Societies concerned in the matter.

The Educational Director will be glad to discuss, in a general way, the problems of an individual veteran member either by correspondence or, preferably, by an interview at College Headquarters.

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Brigadier General Hugh J. Morgan, F.A.C.P., Director of Medical Consultants Division, and Colonel Francis R. Dieuaide, F.A.C.P., Chief of Tropical Disease Treatment Branch, have made an inspection of medical services in the Pacific, Japan and Japanese territory, and have been surveying problems concerned with internal medicine, according to the Office of the Surgeon General of the Army.

During a two-week stop-over in Manila, a special study was made of the comparison between patients from Asia suffering starvation, and Europe's starvation cases. Health studies were recently made in Europe by Brigadier General James S. Simmons, F.A.C.P., Chief of Preventive Medicine Service, and Colonel Thomas B. Turner, Director of Civil Public Health and Nutrition.

## OBITUARIES

## DR. HAROLD DEAN PALMER

Dr. Harold Dean Palmer, F.A.C.P., Philadelphia, Pa.; born, Fairmont, Minnesota, June 12, 1901; attended Culver Military Academy and Hamline University of St. Paul; B.S., 1924, University of Minnesota; M.D., 1927, University of Minnesota Medical School; intern, 1927-29, Philadelphia General Hospital, Philadelphia; Resident Psychiatrist, 1929-31, Pennsylvania Hospital, Philadelphia; Professor of Psychiatry, Woman's Medical College of Pennsylvania; Associate in Psychiatry, University of Pennsylvania School of Medicine; also on the faculty of the University of Pennsylvania Graduate School of Medicine; Senior Psychiatrist, Institute of the Pennsylvania Hospital; Psychiatrist and Consultant in Department for Nervous and Mental Diseases, Pennsylvania Hospital; Visiting Physician and Psychiatrist, Philadelphia General Hospital; Psychiatrist, Health Service, University of Pennsylvania; member, Philadelphia County Medical Society, American Neurological Association, American Psychiatric Association, Philadelphia Neurological Society, Philadelphia Psychiatric Society, American Association for the Advancement of Science, and Research Council on Alcoholism; Fellow, American Medical Association, College of Physicians of Philadelphia, and American College of Physicians (the latter since 1941); Diplomat, American Board of Psychiatry and Neurology; author of numerous published papers, and contributor to *Hughes Practice of Medicine* and *Oxford Medicine*.

Thus is recorded in bare outline the career of a distinguished psychiatrist who died much too soon in Philadelphia on November 20, 1945. His loss will be keenly felt by American medicine. His professional attainments were of the very highest order. He was a careful student and scientific worker and he provided an influence which is very much needed in current psychiatry. His point of view tended to be sanely organic. He exerted a very healthy leavening influence which frequently modified too restricted psychogenic viewpoints and often his careful and verified data were an antidote against overly speculative, armchair thinking.

He was a gentleman in the real sense of the word and in his everyday life, he exhibited true nobility of character. Psychiatry has lost a skilled and constructive advocate and those of us who knew Harold Palmer intimately have lost a dear friend.

EDWARD A. STRECKER, M.D., F.A.C.P.

## DR. ABRAHAM TRASOFF

Dr. Abraham Trasoff, Philadelphia, Pennsylvania, who died suddenly on November 24, 1945 had long been active in the medical affairs of the city.

He received his degree of Doctor of Medicine from the Medico-Chirurgical Medical College in 1915. For the following year he interned at Mount

Sinai Hospital where he had since been closely affiliated. During his association at Mount Sinai Hospital, Dr. Trasoff served as Chief of the Out-Patient Medical Department, Adjunct Visiting Physician, Chief of the Department of Allergy and Attending Visiting Physician.

In addition to his work for the Mount Sinai Hospital, Dr. Trasoff at one time was Clinical Assistant at Jefferson Medical College of Philadelphia and the Jewish Hospital. He was also Consultant in Diseases of the Chest for the United States Veterans Bureau.

Dr. Trasoff closely identified himself with organized medical associations, both local and national. He was a member of many societies and he had been a Fellow of The American College of Physicians since 1940. He had also contributed extensively to the medical literature.

It is with sincere regret that the passing of Dr. Abraham Trasoff is acknowledged.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

#### DR. JULES M. BRADY

Dr. Jules Brady died at his home in St. Louis on September 6, 1945, at the age of 68, after an extremely busy life in the field of pediatrics. Having served, after graduating from medical school, in St. Louis municipal hospitals from 1898 to 1902, he became associated with St. Louis University first in the Department of Pathology; later with the Department of Pediatrics. He was Associate Professor of Pediatrics from 1918 to 1940, when he became Emeritus.

He devoted the greater part of his professional life to the care of infants and small children at St. Ann's Foundling Asylum, and his name is linked in local medical circles with that institution. He was a careful and exacting teacher, and a conscientious physician.

He was a member of the American Academy of Pediatrics, and Diplomate, The American Board of Pediatrics. He was a Fellow of the American College of Physicians since 1920.

RALPH KINSELLA, M.D., F.A.C.P.,  
Governor for Missouri

#### DR. ALPHEUS FELCH JENNINGS

Dr. Jennings was born in Detroit, Michigan, on June 22, 1884. He died of uremia on November 16, 1945.

Dr. Jennings was graduated (A.B.) from the University of Michigan in 1907, and from Harvard Medical School in 1910, following which he served as medical house physician at the Massachusetts General Hospital. At the end of this service he entered private practice in Detroit. For many years he served on the staff of Harper Hospital in Detroit, and since 1936 was Chief of Staff and President of the Board of Trustees of the Charles

Godwin Jennings Hospital. Dr. Jennings' medical interests were wide. He was extramural lecturer in internal medicine at the University of Michigan; Assistant Professor of Clinical Medicine at Wayne University; Consultant in Medicine, U. S. Marine Hospital; former 1st Vice President and Editor of the Transactions, American Therapeutic Society. In addition to these activities he was a Diplomat of the American Board of Internal Medicine, a member of the American Clinical and Climatological Society, and had served as Chairman of the Medical Section of the Michigan State Medical Society, and Vice Chairman of the Medical Section of the American Medical Association. In 1922 Dr. Jennings became a Fellow, American College of Physicians, and, following the death of his father, the late Charles Godwin Jennings, he acted as General Chairman of the 20th Annual Session of the College at Detroit in 1936.

In World War I Dr. Jennings served as Assistant Chief of the Medical Service at Camp Custer and later in France, being discharged with the rank of Major.

The loss of his scientific and clinical abilities will be felt by all who knew and were devoted to him—his patients, students and his associates.

Dr. Jennings is survived by his widow, and three sons: Charles Godwin Jennings II, Capt. M.C., A.U.S., Frederick Anderson Jennings and Richard Hall Jennings, Lt., U. S. Naval Reserve.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

### DR. FERDINAND MICHAEL JORDAN

Ferdinand Michael Jordan, M.D., F.A.C.P., White Plains, New York, died August 14, 1945, at the age of forty-three, of uremia and polycystic kidneys. Dr. Jordan was born at Scranton, Pennsylvania, January 22, 1902; M.D., 1925, University of Pennsylvania School of Medicine; intern, 1925-26, Misericordia Hospital, Philadelphia; postgraduate work at the Mayo Clinic, 1926-1931; M.S. in Medicine, 1929, Mayo Foundation of the University of Minnesota; for many years attending physician, Grasslands Hospital, Valhalla; member of the Associate Staff, St. Agnes and White Plains Hospitals; Diplomat, American Board of Internal Medicine, with special certification in gastro-enterology; member, Kings County Medical Society, New York State Medical Society, and Fellow, American Medical Association.

Dr. Jordan has been a Fellow of the American College of Physicians since 1936. His passing is recorded with deep regret.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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## THE CLINICAL AND ROENTGENOGRAPHIC MANIFESTATIONS OF PRIMARY ATYPICAL PNEUMONIA, ETIOLOGY UNKNOWN\*

By JOHN B. McDONALD,† Captain, M.C., and BERNARD EHRENPREIS,‡ Lieutenant Colonel, M.C., Army of the United States

THE increasing prevalence of atypical forms of primary pneumonia in the past decade has been seriously studied both in civilian and military practice throughout North America, Continental Europe and England. A bronchopneumonia similar to the virus pneumonia so common today was probably first described in 1872.<sup>1</sup> Different names have been applied to this syndrome more recently. Beginning in 1934 Gallagher<sup>2</sup> called it "bronchopneumonia"; later, in 1941, the same author<sup>2</sup> named it "acute pneumonitis." Bowen<sup>3</sup> in 1935 demonstrated by roentgenogram an "acute influenza pneumonitis," while Reimann<sup>4</sup> probably first described and named the entity in 1938 "an acute infection of the respiratory tract with atypical pneumonia." In the same year Francis and Magill<sup>5</sup> demonstrated an unidentified virus producing meningitis and pneumonitis in experimental animals. Smiley and associates<sup>6</sup> illustrated in 1939 "an acute interstitial pneumonia," a new disease entity. At this time Stokes and Kenney<sup>7</sup> demonstrated a new filtrable agent associated with respiratory infections. Then in 1940 Kornblum and Reimann,<sup>8</sup> Kneeland and Smetana,<sup>9</sup> Longcope,<sup>10</sup> and Murray<sup>11</sup> independently described this condition.

In 1942 the nomenclature was designated as "primary atypical pneumonia, etiology unknown," by the Commission on Peumonia of the United States Army.<sup>12</sup> Many excellent reports by numerous authors,<sup>13</sup> either in coöperation with the Army or independently, have been presented.

In view of the scarcity of the clinical and physical manifestations in this disease, the roentgenographic examination has been the most substantial aid in the progress of the study of this condition.

\* Received for publication May 4, 1945.

† Chief, Medical Section, Wm. E. Branch Clinic, Los Angeles, California.

‡ Director, Roentgenology, Kings County Hospital, New York.



The roentgenographic images produced by the pulmonary lesions of atypical pneumonia have been reported by many authors and on analysis appear to be similar, if not identical. Thus, Seeds and Mazer<sup>14</sup> divide the lesions into three main groups: cotton wool, pseudofibrosis and wire glass.

Bowen<sup>3</sup> and Ackermann<sup>15</sup> have drawn attention to the resemblance of certain cases to tuberculosis, especially when located in the upper lung field. These lesions, however, are not sufficiently characteristic of tuberculosis without the supportive evidence of a period of observation. Kornblum and Reimann,<sup>8</sup> studying cases occurring among medical students and nurses dur-

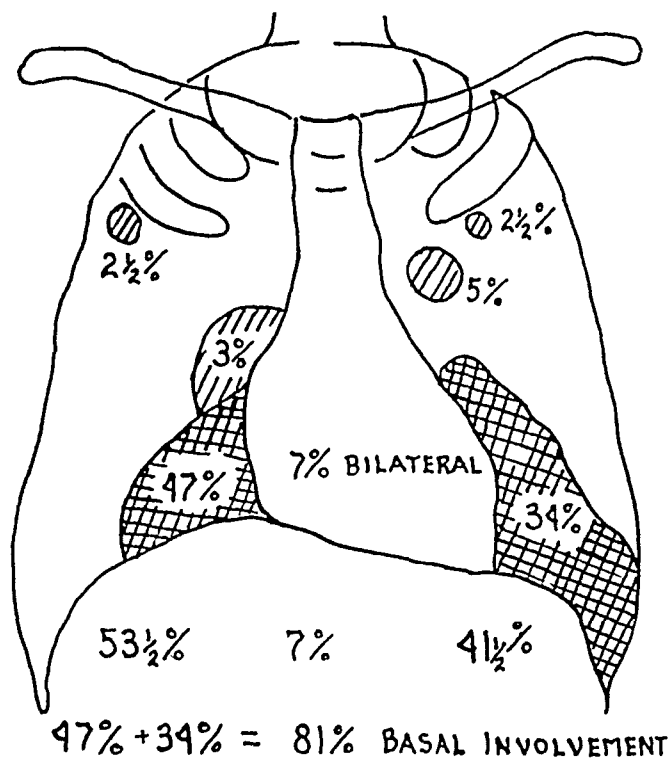


FIG. 1. Diagram representing the percentile frequency of sites of consolidation in a series of 135 cases of primary atypical pneumonia.

ing a mild epidemic of atypical pneumonia, described a picture of acute tracheobronchitis presenting an early stage of this infectious process. They state that the process causes increased density and size of the trunk shadows which are ill-defined and blurred.

From the review of the literature one thing may be clearly noted, i.e., the status of this syndrome has been confusing, and the etiology remains unknown. A clinical study of 75 cases and a radiographic study of 135 cases of primary atypical pneumonia are presented which we feel will aid in the diagnosis of this syndrome.

*Etiology.* The etiology remains unknown. From four cases Weir and Horsfall<sup>16</sup> isolated a filtrable agent in the mongoose which produced pulmonary lesions, and by passage they were able to demonstrate neutralizing

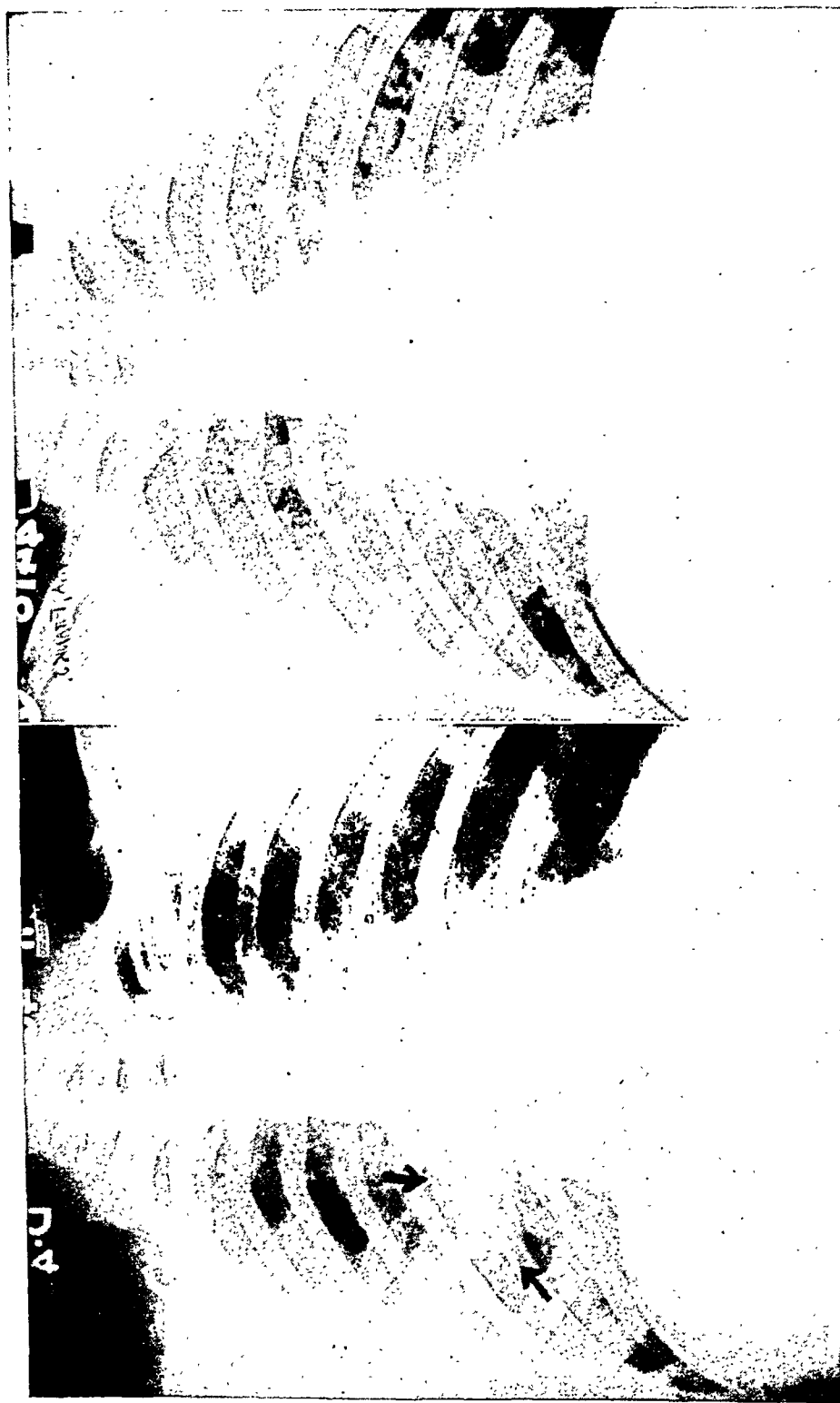


FIG. 2A. A benign circumscribed atypical pneumonia in the right middle lobe.

FIG. 2B. The roentgenogram of the same patient 6 days later, demonstrating a disseminated focal pneumonia throughout both lungs.

antibodies in the serum of convalescent patients. The apparent resistance of some of their animals to infection, and the failure of serial passage to increase virulence have made the results inconclusive. Eaton and his associates<sup>17</sup> obtained a virus that was pathogenic for the hamster and chick embryo, and the cotton rat. The above results have not been confirmed.



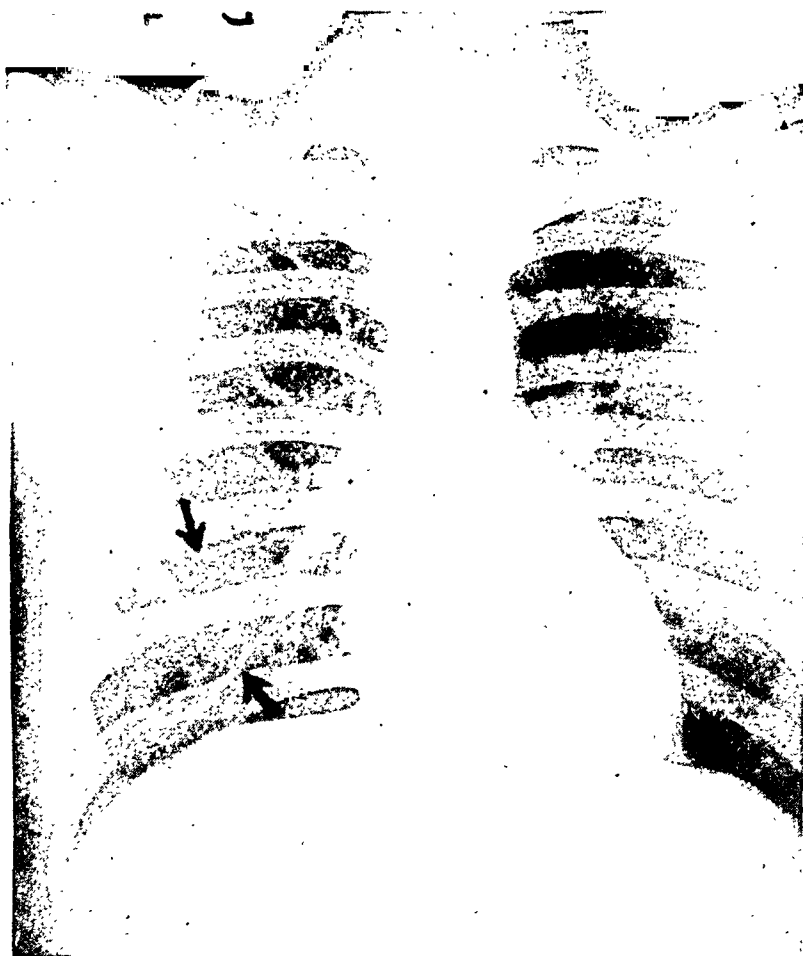
FIG. 2C. The same patient 13 days later with complete resolution.

*Epidemiology.* Although this condition may have existed well back beyond 1872,<sup>1</sup> we feel the current increase is primarily due to the widespread use of roentgenograms. At least three of our patients were discovered only because they were receiving routine physical examinations and were unaware

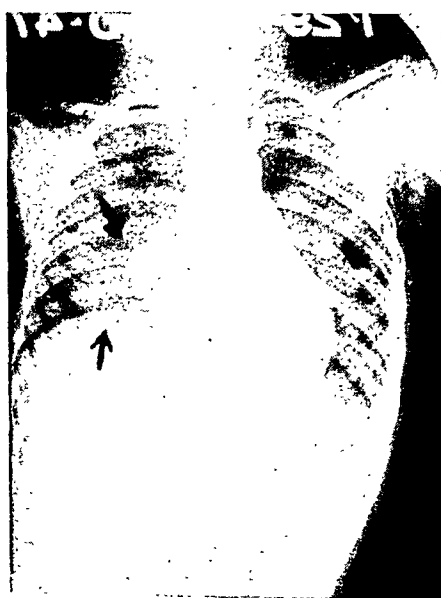
FIG. 3A. A 24 year old father with benign circumscribed type of consolidation in the right lower lobe.

FIG. 3B. His 3 year old daughter with a similar consolidation in the same area.

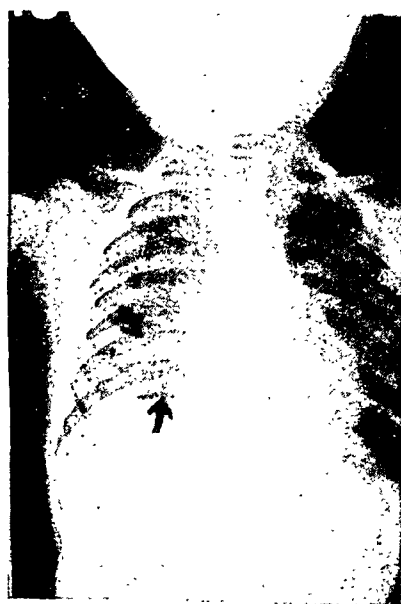
FIG. 3C. His 3 year old daughter with beginning resolution.



A



B



C

FIGS. 3A, 3B, 3C.

of their pneumonic condition, when the examiner, not being satisfied with the chest examination, ordered a routine roentgenogram of the chest. The possibility that sulfonamide therapy has eliminated specific pulmonary infections appears rather questionable, although the sulfadiazine prophylaxis of acute respiratory diseases<sup>18</sup> as recommended by the Army, has reduced the incidence of pneumococcal pneumonia that would follow in the wake of a high rate of acute respiratory diseases. Although it does not appear to be highly contagious, prolonged contacts, such as occur in barracks, college dormitories, and hospitals, have resulted in high incidence of disease, but this may be accounted for by such institutions offering superior controlled studies. Seasonal variation and climate<sup>1</sup> appear to have no influence on the occurrence of this condition.

The age group of our military patients was between 18 and 35 years. There is general agreement that the incidence is high in young adults, as noted in civilian practice by Smith.<sup>19</sup>

### CLINICAL SIGNS AND SYMPTOMS

In an effort to obtain a typical clinical syndrome of primary atypical pneumonia the most frequent symptoms have been tabulated into four groups.

Prodromal symptoms and duration prior to admission to the hospital.

	Percentage of Patients
1. Typical syndrome 1-2 days	47 per cent
2. Pain in chest 2-4 days	40 per cent
3. Previous chest cold and cough 3-10 days	9 per cent
4. No known symptoms	4 per cent

The typical syndrome elicited from 47 per cent of the patients was that of having had a cold from three to 10 days then suddenly developing chills, fever, shortness of breath, cough, headache, sore throat, and generalized aches and pains just prior to admission. The second most common occurrence in 40 per cent of the patients was a history of sharp pain in either side of the chest, or bilateral, aggravated by cough and deep inspiration. Seven per cent in this group had also the symptoms described in Group I. The third group of 9 per cent of the patients gave only a history of about a one to two weeks' duration of a chest cold and moderate cough. The fourth and last group, consisting of 4 per cent of the patients, had no previous history of an upper respiratory infection and were picked up on routine physical examination.

*Temperature.* The range of temperature varied from normal in three patients, to a maximum temperature of 105.6° F.; the latter was limited to the disseminated focal type of pneumonia (figure 2b). The fever usually subsided in two to five days by lysis. The patients rarely looked as sick as their temperature would indicate.

*Pulse and Respiration.* The pulse rate usually corresponded to the temperature level. Intense cyanosis with temporary dyspnea was observed in

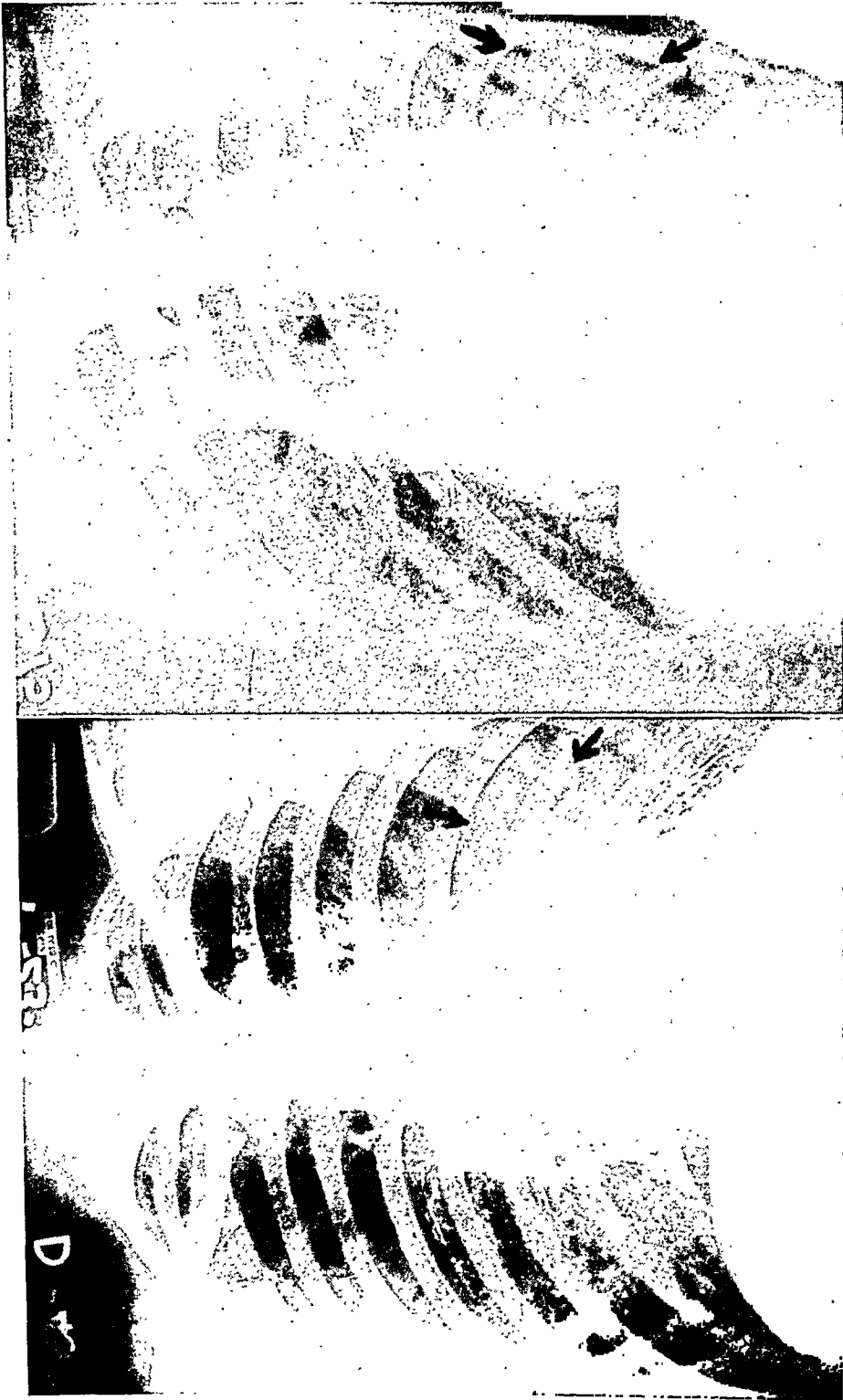


FIG. 4A. Bronchogram illustrating benign circumscribed primary atypical pneumonia of the left pericardial area.

FIG. 4B. Bronchogram illustrating benign circumscribed primary atypical pneumonia of the same case, left oblique projection.

three instances; these patients appeared to have marked relief by oxygen therapy. Asthmatic features were common in about 25 per cent of the patients, occurring commonly when resolution began.

*Physical Signs.* We concur with Smith<sup>10</sup> and others in the fact that the extent of the lesion disclosed by the roentgenogram was usually greater than that anticipated by physical examination. The signs of frank consolidation were usually absent; râles medium and moist in character were found; mild or moderate dullness and suppression of breath sounds were noted in about 70 per cent of the patients having consolidation. Ramsay and Scadding<sup>20</sup> observed that the association of lobar atelectasis with catarrhal infection produces no acute symptoms, and occurs more frequently than recognized.

*Pathology.* The fundamental pulmonic lesion is that of an acute interstitial pneumonitis found at necropsy by Golden,<sup>21</sup> similar essentially to that found in influenzal pneumonitis which has been uncomplicated by secondary bacterial invaders or not unlike that seen in measles pneumonitis. The site of the pathologic process is located about the bronchioles and is filled with pus and desquamated cells from the lining as it is partially destroyed. The bronchiolar walls are heavily infiltrated with round cells and lymphocytes, and markedly edematous. There is a lymphocytic infiltration of the alveolar walls in contrast to bacterial pneumonia, whereas the alveolar spaces frequently contain air. Grossly the lungs of primary atypical pneumonia resemble an acute miliary granulomatous process. In the few cases coming to necropsy reported by Kneeland and Smetana,<sup>9</sup> and Longcope<sup>10</sup> the findings were a patchy hemorrhagic interstitial pneumonia associated with bronchitis and bronchiolitis. Grossly there are areas of atelectasis, emphysema, and gray or red consolidation. The bronchi are filled with mucoid or purulent exudate. Microscopically, there is hemorrhagic infiltration of alveoli with mononuclear cells. The alveolar septa may later show thickening with reduction of the alveolar spaces.

#### ROENTGENOGRAPHIC CHARACTERISTICS

Scadding<sup>22</sup> classifies the pneumonic lesions in primary atypical pneumonia in two main groups: (1) Benign circumscribed pneumonia; (2) disseminated focal pneumonia.

The benign circumscribed variety is fairly well localized, but not sharply defined. It is of uniform density and is located usually in the lower lobes (figure 2a). The disseminated focal type produces pictures of diffuse, rather coarse mottlings, the foci varying from 2 to 5 mm. (figure 2b).

We have found these lesions to be segmental lobular, as have other authors. Only very few cases showed a lobar distribution.

Crysler<sup>23</sup> found that none of the lesions involved an entire lobe even if the posterior anterior view suggested a lobar consolidation. The lateral projection revealed only a part of the lobe as a confluent bronchopneumonia.

Thus an early ill defined localized structural accentuation progresses to a focal or general infiltration and then consolidation.

Aside from other pulmonary conditions this predominantly lobular involvement in atypical pneumonia lends itself to a more convenient morphological and anatomical analysis.

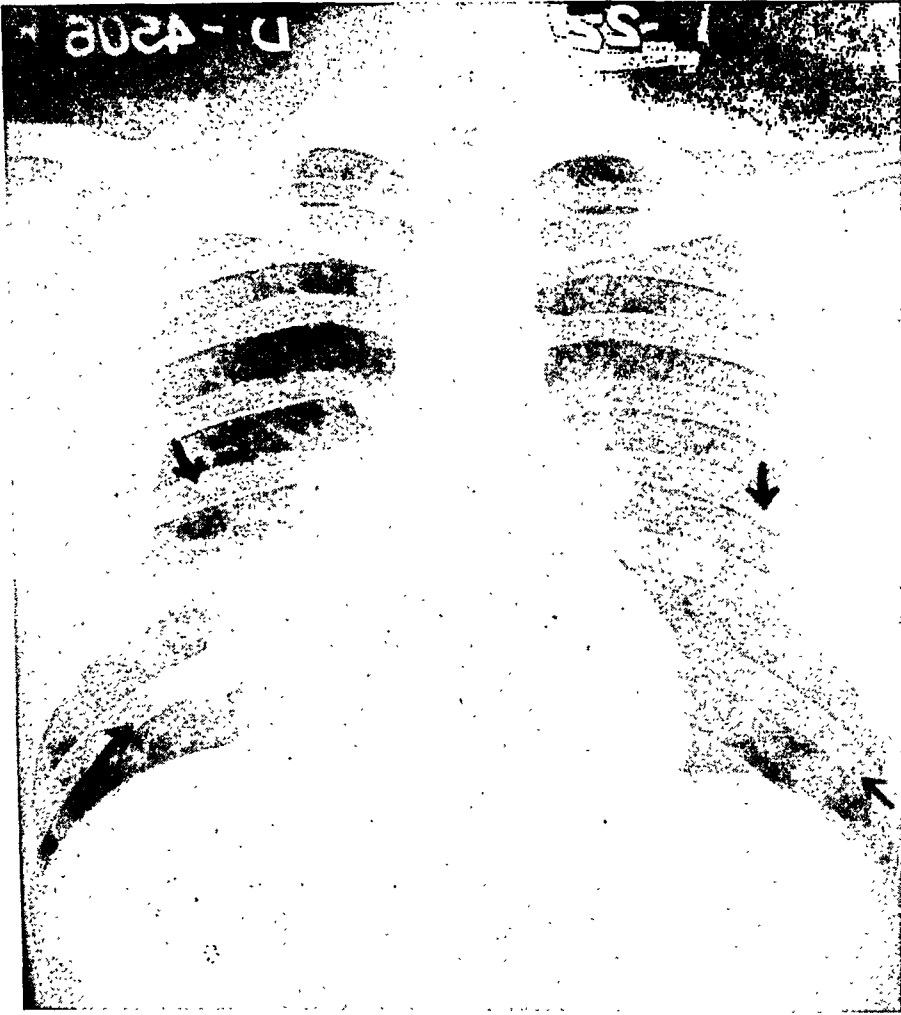


FIG. 5. Benign circumscribed consolidation of right basal lung field and disseminated focal pneumonia left pericardiac area.

Briefly, according to Miller<sup>24</sup> the basic unit of the lung is the primary lobule. It has the form of a truncated pyramid with its base directed toward the periphery of the lung. The primary lobules vary in size from .45 mm. to .845 mm. The larger units are situated in the peripheral and basal portions of the lung. The secondary lobule comprises 50 to 250 of these lobules. Depending upon the size and thickness of the perilobular septum many a structure corresponding with the shape of the lobule can be seen on the normal roentgenogram. In inflammatory conditions the transparent



(black) lobules are surrounded by (gray) increasingly thickened perilobular septa until the lobules disappear, either due to collapse or exudate, thus leading to the picture of consolidation (figures 6a, 6b). The conspicuous feature appears to be the engorgement of the perilobular structures or septa, which is seen in the initial stages and persists around the reilluminated lobule during the resolution of the process.

The resolution is manifested by irregular thinning of the septa, or interstitial tissues, thus enabling the air to be seen again in the lobule (figures 6a, 6b). The condition can be differentiated by increased sharpness of the perilobular septa and reillumination of the lobules. The time of resolution varied with the size of involvement from six days to six weeks usually. The average time of complete resolution did not exceed 16 days.

The differential diagnosis between atypical pneumonia and pulmonary tuberculosis and/or primary pulmonary coccidioidomycosis offers little difficulty in view of the comparatively infrequent involvement of the upper lobes in atypical pneumonia (5 per cent) and the rapidity of resolution of this process. The pulmonary tuberculous lesions present elements of fibrosis, calcification, and exudation due to the chronicity of the lesion. In the review of the cases of primary pulmonary coccidioidomycosis by the authors<sup>25</sup> no calcification of the lesions has been found. The prominent non-calcified hila in primary pulmonary coccidioidomycosis offer another differential diagnostic feature. Laboratory aids are discussed below.

This morphological analysis of the cases is in conformity with the pathological findings and appears to be more adequate than the generally used terms "bronchial" or "peribronchial." The fairly uniform size of the lobule throughout the lungs offers a concrete visible part of the respiratory system in contrast to the diminishing bronchi which cannot be recognized in the periphery without the aid of a microscope. These lobular and perilobular manifestations of the lung are of even greater aid in the differentiation of other pulmonary conditions which are beyond the scope of this paper. The use of the terms "lobular" and "perilobular" seems, therefore, to be indicated in the detailed study of lung pathology.

The basal involvement, consisting of consolidations lodged in the cardiophrenic angle, has been a predominant feature in over 80 per cent of these cases (figures 1, 2a, 3a, 3b, 3c, 4a, 4b). The claim<sup>13</sup> that the ambulatory attitude of the patient may be responsible for the basal manifestation of the disease remains conjectural.

Of the disseminated focal type there were nine cases, or 7 per cent, encountered in the 135 cases (figure 2b). In 47 per cent of the patients the involvement occurred in the right base; in 34 per cent of the patients it appeared in the left base. In 12 patients, or 17 per cent, the upper and middle

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FIG. 6A. (*above*) Resolving benign circumscribed type of atypical pneumonia with characteristic lobular and perilobular arrangement in the right cardiophrenic area. (*below*) Mesial lung field: A. Perilobular tissues (septum), gray. B. Secondary lobule, black.

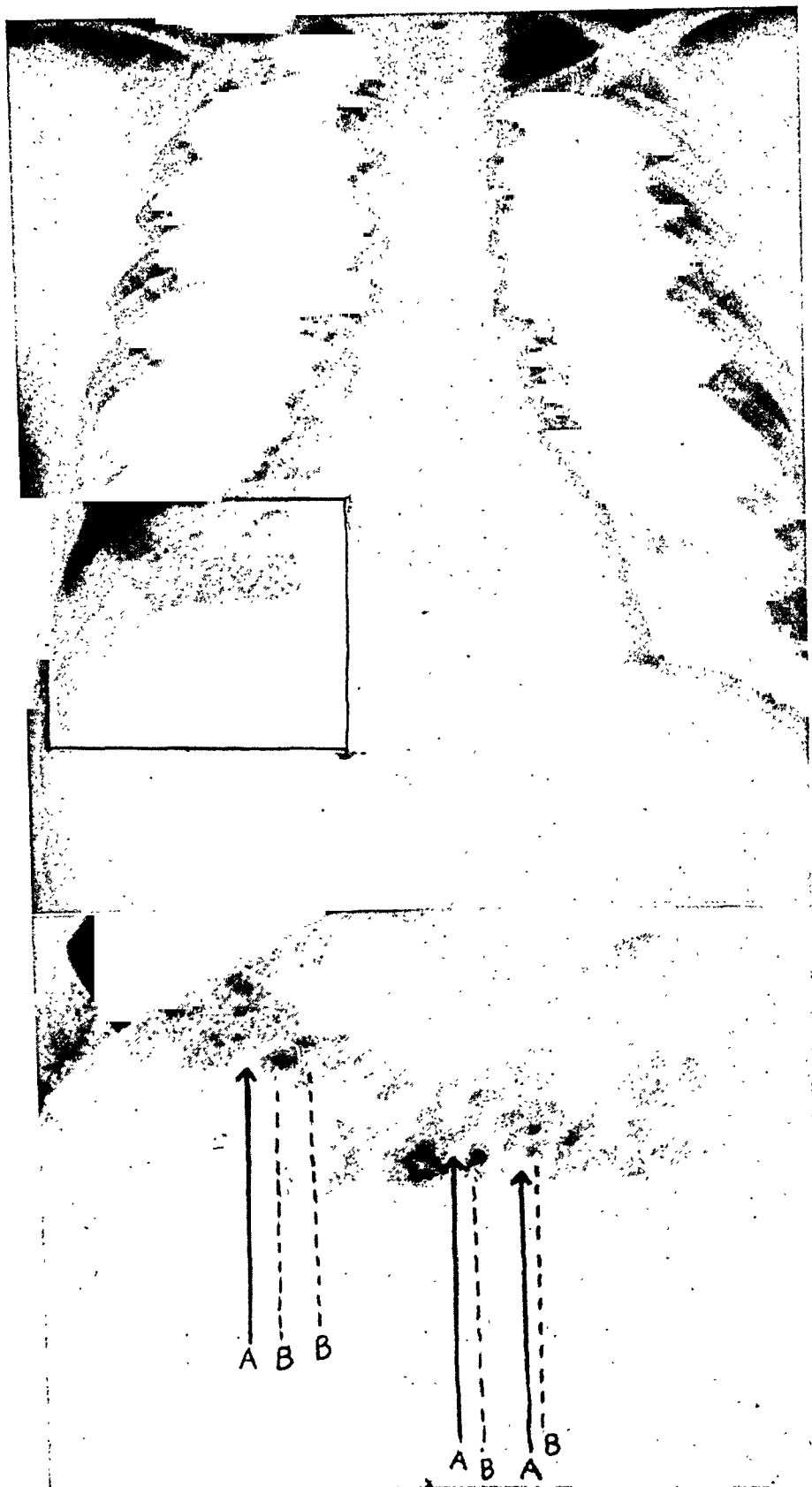


FIG. 6A.

lung fields were involved. Only nine patients developed slight pleural effusion, one a moderate effusion requiring prolonged hospitalization, and three solitary lung abscesses which healed spontaneously.

### LABORATORY AIDS

*Sputum.* Productive cough with copious sputum was present at the onset in about 30 per cent of the cases, whereas in 70 per cent it started with resolution. Seven patients had blood-streaked sputum at the onset of the illness, but the most common was the mucopurulent type. Sputum smears were made in 95 per cent of the cases. Specific typing sera for pneumococci were employed in each; but only 15 per cent of the cases gave positive Quellung reactions, which invariably were with the high numbered groups. In differentiating pulmonary tuberculosis repeated sputum examinations were required on numerous patients.

*Blood.* The hematologic studies revealed that the leukocyte count was normal in the majority of cases, as demonstrated in figure 7 showing the initial count in 75 patients. The neutrophils and monocytes were slightly increased in number, and a lymphopenia was common. Blood cultures were all negative. Leukocytosis was usually associated with secondary bacterial invasion.

*Cold Agglutinins.* A study of autohemagglutinins or cold agglutinins was made on 12 patients only. They were positive in low titer in eight, positive in high titer in two, and negative in two. Sera were stored before examination, a fact which might account for the low titers. Complement fixation for elementary type of virus was demonstrated in low titer in two of the patients that were negative for cold agglutinins. Repeated blood examinations during convalescence eight to 14 days after onset of illness<sup>26</sup> for demonstration of cold agglutinins were not practicable because of the early recovery of a majority of the cases.

*Urine.* Transient albuminuria was present only in those patients with high temperatures; hyaline and granular casts were present in a small percentage of these. Blood chemistry remained normal. Transient hematuria was observed in four patients treated with sulfadiazine; uneventful recovery ensued.

*Sedimentation Rate.* The modified Cutler method of determining the sedimentation rate with a normal of 10 mm. in 60 minutes was employed. Rates were obtained usually on the fourth day after admission. Additional sedimentation rates were taken, and as demonstrated in figure 8 the highest acceleration of the erythrocyte sedimentation test varied considerably in 75 patients. On discharge all patients had a rate less than 15 mm. in 60 minutes. It was found in 10 per cent of the patients that the sedimentation rate

FIG. 6B. (*above*) Identical lobular and perilobular pattern in right costophrenic lung area. (*below*) Peripheral lung field: A. Perilobular tissues (septum), gray. B. Secondary lobule, black.



FIG. 6B.

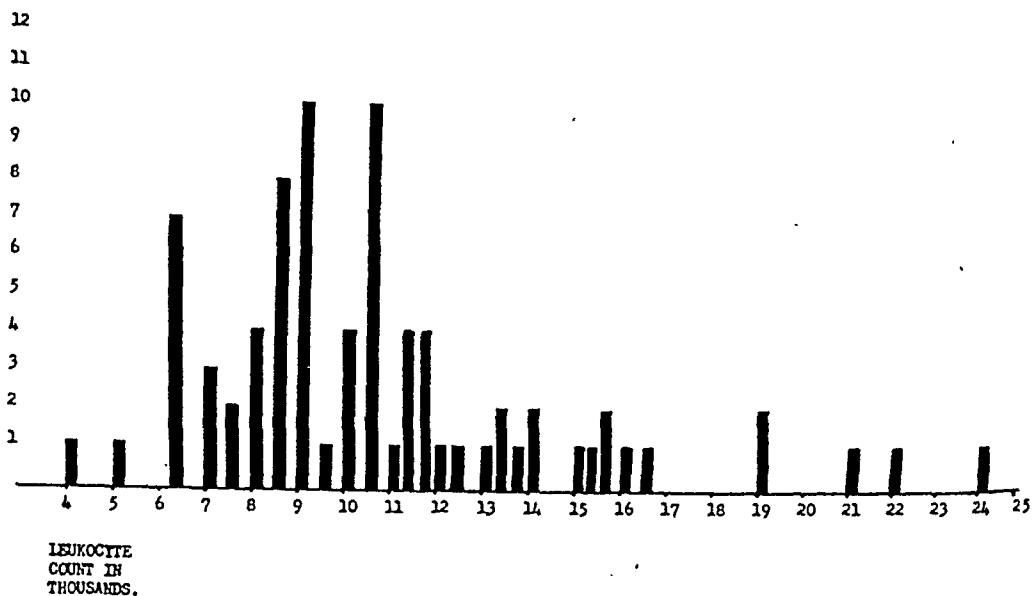
NUMBER OF  
PATIENTS

FIG. 7. Initial leukocyte count of 75 patients with primary atypical pneumonia.

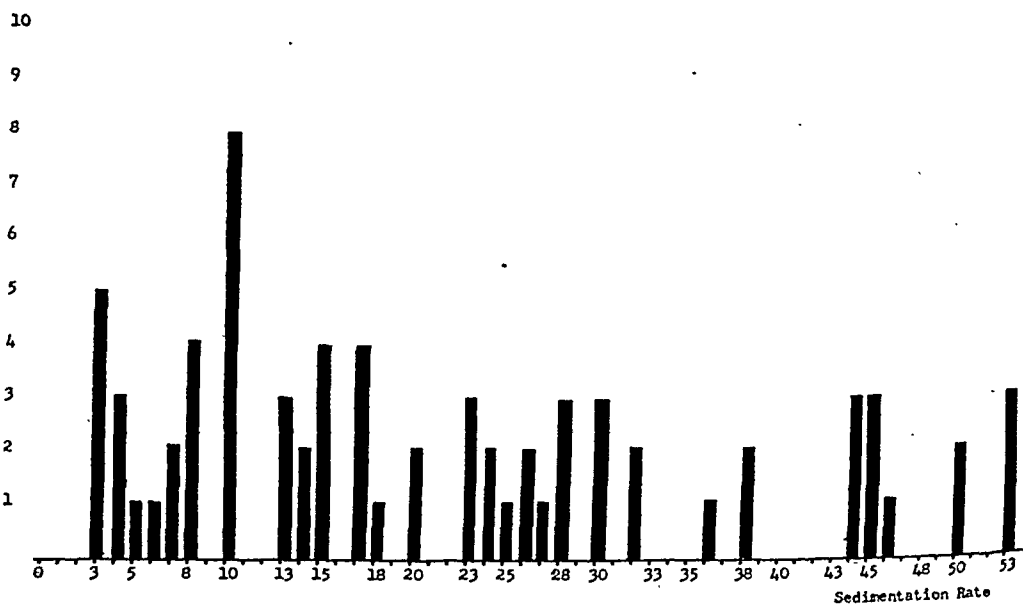
NUMBER OF  
PATIENTS

FIG. 8. Highest peak in sedimentation rate of 75 patients with primary atypical pneumonia.

had become normal, although resolution was not complete by roentgenogram. It was also noted that sedimentation rates remained normal in over 21 per cent of the patients with minimum consolidation.

*Tuberculin Patch Test.* The Vollmer patch test was used in those cases in which resolution was slow or linear lesions persisted by roentgenogram.

The percentage of positive patch tests in this series equaled that found in the general population.

*Coccidioidin Skin Test.* Coccidioidin skin tests were made on those patients in which resolution was slow, or the hilar distribution was indicative, and on those patients who gave a history of having been in an endemic area. When the tests were positive, reactions of more than 5 mm. in 48 hours,<sup>25</sup> blood precipitin and complement fixation serologic tests were performed by Dr. C. E. Smith of Stanford School of Medicine. No cases of active primary pulmonary coccidioidomycosis were found in these patients.

#### COMPLICATIONS

Nine patients developed slight pleural effusion, which consisted of mere blunting of the costophrenic angle, and rapidly recovered. One patient developed a moderate effusion which required extensive hospitalization. Three patients developed single lung abscesses, probably from secondary pyogenic invaders; all healed spontaneously with uneventful recovery. No deaths occurred among these patients.

#### TREATMENT

So far, treatment has been symptomatic. Oxygen was used liberally where cyanosis and dyspnea were present. Bed rest is essential even in the mildest case. Codeine, throat irrigations, expectorants, steam inhalation, and sedatives are necessary and welcome when the cough is non-productive and painful. Fluids were forced. In uncomplicated cases of primary atypical pneumonia, penicillin and sulfonamides were of no value. Among our patients, penicillin was used in six, and sulfadiazine was used in 18 patients; there was satisfactory response in all. These patients, however, had secondary invasion by pyogenic bacteria, manifested by increasing numbers of pyogenic organisms in the sputum, an abrupt rise in leukocyte count, chills and fever, and usually evidence of roentgenographic spread. Of the six patients treated with penicillin one was sensitive to sulfonamides.

#### SUMMARY

1. A clinical study of 75 cases and roentgenographic manifestations of 135 cases of primary atypical pneumonia have been described.
2. The salient clinical symptoms were tabulated into four groups.
3. The extent of the pulmonary lesion by roentgenogram is much more extensive than that anticipated by the physical examination, therefore, mild cases may be overlooked if radiographs are not taken.
4. The similarity of primary pulmonary coccidioidomycosis and, to a much lesser degree, pulmonary tuberculosis, requires consideration to avoid error.
5. Roentgenographic manifestations along the more simple "lobular" than hitherto "bronchial" morphology have been postulated and discussed.

6. Normal sedimentation rates are not alone conclusive of complete resolution, therefore, serial roentgenograms will have to be employed.

7. The hematologic studies usually revealed a lymphopenia while the leukocyte count was normal in the majority of cases.

8. The disease has a high morbidity but a low mortality with infrequent complications. In 135 patients, nine developed slight pleural effusions, one of which became moderate requiring prolonged hospitalization; three patients developed solitary lung abscesses which healed spontaneously.

Acknowledgment: We wish to express our appreciation for the photographic aid given by Private First Class Richard H. Dale.

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# THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN: SECOND REPORT \*

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IN a recent communication <sup>1</sup> the authors reported on the use of penicillin in the treatment of subacute bacterial endocarditis. Of 20 patients in whom the infecting agent was a streptococcus sensitive to the action of the drug, 15 apparently recovered; two were rendered free of infection as long as therapy was continued but subsequently relapsed; three succumbed. In the majority of cases, heparin was employed as an adjuvant to penicillin, but it was felt that further experience was necessary before an opinion could be expressed as to the value of this form of anticoagulant therapy. It was also realized that a further follow-up was desirable in many of the patients who had been observed for only a comparatively short period after treatment had been discontinued.

With the increase in the available supply of penicillin, it became possible to treat by more intensive methods the two patients in the previous series who relapsed after treatment had been discontinued, and to extend treatment to a further series of 15 patients. On the basis of this additional experience an appraisal of the value of heparin has now been made and a regimen is tentatively proposed for the future treatment of patients with this disease. Furthermore, the 15 "recovered" patients in the first series have now been followed for an additional 10 months.

## PART I: RESULTS OF MORE INTENSIVE PENICILLIN THERAPY IN TWO PATIENTS WHO RELAPSED

In the previous communication it was reported that two patients with subacute bacterial endocarditis (Cases 16 and 17) had relapsed shortly after penicillin therapy was discontinued. Since further intensive treatment provided information of the greatest value in formulating an effective therapeutic regimen for other cases of this disease, the course of this treatment with the results is here presented in detail.

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The penicillin was provided in part by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council, and in part by Mr. John L. Smith, President of Chas. Pfizer & Company, Brooklyn, N. Y.

† Died April 27, 1945.

Of these two patients, one (Case 16) had received 36,700,000 units in four courses extending over a period of five months; the other patient (Case 17) received 18,390,000 units in four courses over a period of four months. The maximum daily dose which had been administered to the former was 500,000 units and to the latter 320,000 units. Both patients had received heparin for prolonged periods. In spite of their protracted illness and the presence of positive blood cultures when treatment was interrupted, both patients remained in remarkably good clinical condition.

*Case 16.* O. M. (additional report). On October 15 treatment was resumed. One million units of penicillin were given daily by continuous intramuscular drip for 21 days and the same amount by continuous intravenous drip for a further period of seven days. In addition 4 gm. of sulfadiazine were administered daily. The blood was not heparinized. Penicillin serum levels averaging 0.28 unit per cubic centimeter were maintained throughout. The patient tolerated the procedure remarkably well except for an unexplained episode of pyrexia on the last day of therapy. The temperature gradually returned to normal but there was only moderate subjective improvement and, in spite of frequent transfusions, there was a persistent anemia. For a week after therapy had been discontinued, the temperature remained normal but two days later the blood culture was again positive, and on the same day petechiae were observed. In the succeeding 10 days the temperature gradually rose to 101–102° F., and the clinical condition became worse. Sensitivity tests revealed that, although the infecting strain was perhaps slightly more resistant to penicillin than it had been originally, no striking change had occurred. Accordingly, a further attempt to terminate the infection was made. On November 30 penicillin therapy was resumed and 2,000,000 units were given daily by continuous intramuscular drip for fourteen days. Heparin was not employed. Throughout the period of therapy, the temperature remained between 100–102° F., and there was considerable pain at the site of the infusion. Penicillin serum levels ranged from 0.56 to 4.48 units, usually remaining between 1.12 and 2.24 units per cubic centimeter. After two weeks, treatment was discontinued to permit evaluation of the situation. During the following week the temperature remained below 100° F., blood cultures were sterile, and the patient was allowed up in a wheelchair. On December 22 the patient was discharged. Since then he has continued to be afebrile, and blood cultures have remained sterile. At the time of the last follow-up, August 10, he had gained 16 pounds (7.2 kg.) and had returned to work.

*Case 17.* M. K. (additional report). On November 9, penicillin therapy was resumed, 500,000 units daily by continuous intramuscular drip. The clinical response was immediately favorable, but on the seventh day the temperature rose to 103.6° F., with intense pain and soreness at the site of injection. Therapy was accordingly discontinued. The clinical course continued favorable, but 12 days later a positive blood culture was again obtained. Five hundred thousand units daily by continuous intramuscular drip were resumed on December 1 and continued for 14 days. During this period the treatment was well tolerated, and the course continued to be quite uneventful until the ninth day after cessation of therapy when the blood culture was again positive. It seemed obvious, therefore, that more intensive therapy was required. Accordingly the patient was permitted to return home on maintenance doses of sulfadiazine until the necessary arrangements could be made for resumption of penicillin therapy. During the first three weeks she remained afebrile and gained 7 pounds (3.1 kg.) in weight, but during the fourth week several minor embolic episodes occurred. On January 29, 1945, she passed a moderate sized embolus to one of the branches of the right posterior tibial artery. On January 30 she was read-

mitted and therapy was resumed, 1,000,000 units daily by continuous intramuscular drip for 12 days. Throughout this period she continued to run an irregular fever, but this was attributed to irritation at the site of the infusion. As soon as penicillin was discontinued, the temperature promptly returned to normal, blood cultures remained sterile, and convalescence proceeded uninterruptedly. The only untoward symptoms have been slight pain, numbness and a tingling sensation in the foot where the embolus occurred. The patient has since married and is leading a normal life.

*Discussion of Cases 16 and 17.* From the results of therapy in these two cases several points of interest emerge. It was observed that, in difficult cases, maintenance of penicillin serum levels equivalent to twice the amount required to inhibit growth of the infecting streptococcus in vitro might not result in a cure of the patient, even though treatment were continued for as long as four weeks, whereas in both cases intensive therapy with larger daily doses over periods of 14 and 12 days respectively resulted in apparent recovery. Furthermore, although heparin had been used in conjunction with penicillin during the previously unsuccessful courses of therapy, the infection in both patients was eventually terminated by the use of penicillin alone.

As the result of the observation made on the two subjects, it was decided to try shorter and more intensive courses of treatment with penicillin alone in a series of patients.

## PART II: RESULTS OF SHORT INTENSIVE PENICILLIN THERAPY IN THE TREATMENT OF 15 ADDITIONAL PATIENTS

*Selection of Cases.* The cases in this group represent consecutive hospital admissions of patients with a diagnosis of subacute bacterial endocarditis. With one exception (Case 30), in every case the infecting organism was a *Streptococcus viridans* or a non-hemolytic streptococcus. Numerous positive blood cultures were obtained before treatment was instituted in all cases. Every patient had murmurs indicative of organic heart disease and most of them showed embolic phenomena, splenomegaly, anemia and microscopic hematuria.

*Methods of Penicillin Administration and Course of Therapy.* Penicillin was administered for the most part by constant intramuscular drip, either through a No. 19 to No. 22 needle inserted into the quadriceps femoris muscle, or in some cases through a flexible plastic tube<sup>2</sup> similarly inserted into the thigh. In the majority of cases penicillin serum levels were determined daily. A 24 hour volume of 250 to 500 c.c. of penicillin solution in 0.85 per cent sodium chloride was well tolerated whereas larger volumes appeared to cause pain by mechanical distention of the muscle. The site of infusion was usually changed from one thigh to the other every 48 or 72 hours depending on the amount of local reaction, but in some instances an infusion was run continuously into one site for as long as seven days without causing any marked local reaction. The majority of patients, however, complained of slight discomfort in the muscle and many showed mild swelling, redness and heat locally. Although temperatures of 100–102° F.,

apparently caused by reaction to the infusion, were not uncommon during therapy, only once was it necessary to stop treatment because of hyperpyrexia, and there the reaction was apparently due to the particular lot of penicillin used, inasmuch as a subsequent course of therapy by the same route using larger doses of a different lot of penicillin was entirely uneventful.

Blood cultures almost invariably were sterile during therapy, though often the patients continued to look and feel ill. The erythrocyte sedimentation rate remained elevated in the majority of cases until several weeks after cessation of treatment, probably owing in part to the tissue reaction to intramuscular infusion. Major peripheral emboli were uncommon in this group. One patient had a cerebral embolus with hemiplegia during treatment. In one case a small embolus to the cerebrum, resulting in loss of part of the visual field, occurred three weeks after therapy. Blood cultures from this patient have been repeatedly sterile and there has been no evidence of recurrence of the infection during a follow-up period of six months.

Relapses after interruption of therapy have occurred in a number of patients, but it is to be noted that in no case observed to date has the infection recurred later than two weeks after treatment. In no case as yet has the infecting organism developed significant resistance to penicillin even though in one patient (Case 16) relapses occurred repeatedly over a period of six months during which time he was receiving inadequate doses of the drug.

Because the clinical course of these patients under therapy has been so variable, it appears impossible to assess at any time during treatment the success or failure of a particular course of penicillin. It has in fact been necessary to rely upon previous clinical experience in planning a course of treatment and in deciding arbitrarily upon the time to stop. Observation of the patient's general condition and of the blood cultures after cessation of therapy has proved to be the only satisfactory means of determining whether or not further treatment is indicated.

The daily dose of penicillin has varied from 200,000 to 2,000,000 units, depending upon the sensitivity of the infecting organism and upon the serum levels obtained. In general, an attempt has been made to maintain serum penicillin levels at least four times the amount required to inhibit growth of the organism *in vitro*.

The chief pertinent data relating to these patients are summarized in table 1. Detailed case histories are presented below of 8 patients selected to show the variations in the clinical course encountered in the group.

*Case 21.* R. L., a woman aged 21, known to have had rheumatic fever, had been admitted 10 weeks previously to another hospital where a diagnosis of subacute bacterial endocarditis was made, 100,000 units of penicillin were administered intramuscularly each day for three weeks with some improvement, but fever recurred when treatment was stopped. On September 1, 1944, she was transferred to the Presbyterian Hospital. On admission she was a frail, delicate, wasted girl, acutely and chronically ill, with fever of 102–104° F., pulse 110–130, mitral stenosis, palpable spleen, clubbed

fingers and painful fingertips. Five blood cultures were positive for *Str. viridans*, which was one quarter as sensitive to penicillin as the standard strain of hemolytic streptococcus (C203 Mv). Starting on September 6, 25,000 units were given every three hours intramuscularly, and on the twelfth day, because a blood culture taken three days previously was positive, the dosage was increased to 40,000 units every three hours. This regimen was continued 13 days more making a total of 6,330,000 units. Heparin was administered subcutaneously, 100 mg. approximately twice a week. Throughout the entire period of therapy the patient failed to show significant improvement. She continued to have an irregular fever, passed numerous small emboli and on several occasions had alarming episodes of paroxysmal tachycardia. Two days after cessation of penicillin the blood culture was again positive and on October 6 therapy was resumed. On this occasion, 300,000 units daily were administered by continuous intramuscular drip. After an initially satisfactory clinical response, organisms were once more recovered in one of two flasks of a blood culture taken on the eleventh day, and about the same time there was a recurrence of low-grade fever. Penicillin was continued for 12 days longer, and since the organism was also sensitive to sulfonamides, sulfadiazine was given during the last seven days. Penicillin was discontinued after 23 days to permit evaluation of the situation. Three days later the patient developed auricular fibrillation and was digitalized. Sulfadiazine was continued for three weeks. In the month following, she remained afebrile and blood cultures were sterile. She continued to gain in strength, the erythrocyte sedimentation rate returned to normal, and on December 1 she was discharged to a convalescent home.

During the following six months the patient remained free from signs or symptoms of infection, although she had a marked decrease in cardiac reserve. Blood cultures taken on January 29 and March 30 were sterile and the sedimentation rate remained normal. On May 28 she complained of pain in the cardiac area, but had no other symptoms. The following morning she was found dead. An autopsy was performed eight hours later. The cause of death was not determined but the heart was greatly enlarged and showed severe mitral stenosis. On the mitral valve were several small vegetations which on microscopic section showed no bacteria and no acute inflammatory reaction. Although a *Streptococcus viridans* was cultured from the heart's blood at post mortem eight hours after death, it appeared to be different from the strain recovered from the blood during the patient's illness. The postmortem strain grew in the form of large, smooth, grayish-white colonies on blood agar and produced diffuse clouding in liquid medium. The original strain, on the other hand, produced small matt colonies on blood agar and a coarsely granular type of growth in broth. Rabbit antiserum prepared with the original strain and containing agglutinins in high titer against this strain failed to agglutinate the organism recovered at autopsy. Furthermore, the postmortem strain was 10 times as sensitive to penicillin as the original organism. It was therefore concluded that the patient had been cured of the infection and that the organism grown from the heart at autopsy was either a contaminant or represented a postmortem invasion of the blood.

Case 24. W. B., a man aged 33, known to have had rheumatic fever at the age of 7 with several recurrences in succeeding years, began to have easy fatigability, vague pains and anorexia in July 1944. In the following two months he lost 10 pounds in weight, had fever and noticed painful fingertips. On admission September 18, he had conjunctival petechiae, mitral and aortic rheumatic heart disease, palpable spleen and clubbed fingers. *Str. viridans*, twice as sensitive to penicillin as the standard strain, was cultured from the blood. Penicillin therapy was started on September 29, 200,000 units daily by constant intramuscular drip for 21 days. Heparin was not employed. After the third day of therapy, blood cultures were sterile and the temperature remained below 100° F. The erythrocyte sedimentation rate dropped

TABLE I  
The Treatment of 17 Cases of Subacute Bacterial Endocarditis with Penicillin

Case No.	Pt. Age Sex	Primary Cardiac Disease	Probable Duration of Infection	Infecting Organism		Penicillin				Average Blood Level, U/c.c.	Result	Follow-up 9/1/45
				Type	Sensitivity to Penicillin, Units per c.c.*	Dates of Therapy	Dose in Units and Route	No. Days	Total per Course and per Patient			
16	O. M. M-30	Rheum. aortic and mitral	7-8 mos.	<i>Strep. vir.</i>	0.14	a, b, c, d <sup>1</sup> (e) 10/15/44-11/11/44	1,000,000 IM drip or IV drip	103	36,700,000 <sup>1</sup>	.28	Recov.	8 mos.
						(f) 11/30/44-12/14/44		28	28,000,000			
17	M. K. F-21	Rheum. mitral	7 mos.	<i>Strep. vir.</i>	0.035 0.07 0.07	a, b, c, d <sup>1</sup> (e) 11/ 9/44-11/16/44 (f) 12/ 1/44-12/14/44 (g) 1/30/45- 2/10/45	500,000 IM drip 500,000 IM drip 1,000,000 IM drip	14	28,000,000	.14 .28 .56	Recov.	7 mos.
								145	92,700,000			
								85	18,390,000 <sup>1</sup>			
								7	3,500,000			
21	R. L. F-21	Rheum. mitral	3 mos.	<i>Strep. vir.</i>	0.07 0.2	(a) 9/ 6/44- 9/30/44 (b) 10/ 6/44-10/28/44	25-40,000 q3h IM 300,000 IM drip	24	6,330,000	.14	Died†	11 mos.
								23	6,900,000			
22	E. B. M-45	Rheum. aortic	3½ mos.	<i>Strep. vir.</i>	0.035	9/16/44-10/ 7/44	300,000 IV drip	47	13,230,000	.07	Recov.	11 mos.
23	W. D. M-35	Rheum. aortic	2 wks.	<i>Strep. vir.</i>	0.035-0.017	9/22/44-10/13/44	200,000 IV drip	21	4,300,000	.03	Recov.	11 mos.
24	W. B. M-33	Rheum. mitral	3 mos.	<i>Strep. vir.</i>	0.008	9/29/44-10/20/44	200,000 IM drip	21	4,200,000	.03	Recov.	10 mos.

\* Sensitivity of *Str. hemolyticus* C203Mv = 0.017 U/c.c.

TABLE I—Continued

Case No.	Pt. Age Sex	Primary Cardiac Disease	Probable Duration of Infection	Infecting Organism		Penicillin				Average Blood Level, U/c.c.	Result	Follow-up 9/1/45
				Type	Sensitivity to Penicillin, Units per c.c.*	Dates of Therapy	Dose in Units and Route	No. Days	Total per Course and per Patient			
25	S. M. M-36	Rheum. aortic and mitral	5 wks.	<i>Strep. vir.</i>	0.14-0.28	(a) 11/ 1/44-11/10/44	500,000 IM drip	10	5,000,000	.14	Recov.	8 mos.
					0.14-0.28	(b) 11/30/44-12/11/44	500,000 IM drip	10	5,000,000	.28		
					0.28	(c) 12/29/44- 1/11/45	1,000,000 IM drip	14	14,000,000	.56		
26	H. G. M-42	Congen. patent ductus arter.	8½ mos.	<i>Strep. vir.</i>	0.035	11/20/44-11/29/44	500,000 IM drip	10	5,000,000	.14	Recov.	9 mos.
27	R. J. M-21	Rheum. aortic and mitral	6 wks.	<i>Strep. vir.</i>	0.017	12/ 1/44-12/10/44	200,000 IM drip	10	2,000,000	.07	Recov.	9 mos.
28	J. G. M-28	Rheum. aortic and mitral	3 mos.	<i>Strep. vir.</i>	0.07	12/13/44-12/22/44	500,000 IM drip	10	5,000,000	.28	Recov.	8 mos.
29	H. B. M-51	Rheum. mitral	9 mos.	Indiff. <i>Strep.</i>	0.035	12/29/44- 1/ 8/45	500,000 IM drip	10	5,000,000	.56	Recov.	8 mos.
30	M. M. M-16	Congen. ? type	19 mos.	Micro-aerophilic micro-coccus	approx. 0.017	1/18/45- 1/27/45	500,000 IM drip	10	5,000,000	.28	Recov.	7 mos.
31	H. L. M-59	Congen. vent. septal defect	6 wks.	<i>Strep. vir.</i>	0.035-0.017	2/26/45- 3/ 7/45	500,000 IM drip	10	5,000,000	.2	Recov.	6 mos.

TABLE I—Continued

Case No.	Pt. Age Sex	Primary Cardiac Disease	Probable Duration of Infection	Infecting Organism		Penicillin				Average Blood Level, U/c.c.	Result	Follow-up 9/1/45
				Type	Sensitivity to Penicillin,* Units per c.c.*	Dates of Therapy	Dose in Units and Route	No. Days	Total per Course and per Patient			
32	M. B. F-13	Congen. ? vent. septal defect	5 mos.	Indiff. strep.	0.017	(a) 3/ 5/45- 3/13/45	200,000 IM drip	7	1,400,000	.03	Recov.	3 mos.
						(b) 3/22/45- 4/ 1/45	500,000 IM drip	10	5,000,000			
						(c) 4/16/45- 4/29/45	1,000,000 IM drip	14	14,000,000			
						(d) 5/15/45- 6/11/45	500,000 IM drip	28	14,000,000			
33	E. A. M-50	Rheum. aortic and mitral	7 mos.	Indiff. Strep.	0.035	3/26/45- 4/ 7/45	500,000 IM drip	13	6,500,000	.4	Died†	
34	E. P. F-37	Rheum. mitral	6 mos.	<i>Strep. vir.</i>	0.07	(a) 4/ 6/45- 4/19/45 (b) 4/29/45- 5/ 5/45	500,000 IM drip 25,000 q3h IM (operation)	14	7,000,000	.2	Recov.	4 mos.
								6	1,150,000			
								20	8,150,000			
35	O. B. F-23	Congen. patent ductus arter.	9 mos.	<i>Strep. vir.</i>	0.035	4/13/45- 5/ 1/45	500,000 IM drip	19	9,500,000	.2	Recov.	4 mos.

† Died of heart failure. No evidence of active infection at autopsy.



from 63 to 14 mm. in one hour, and on November 12 the patient was discharged to convalesce at home. Since then he has resumed his occupation as an office worker and has remained entirely free of symptoms. Repeated blood cultures have been sterile.

*Case 25.* S. M., a man aged 36, had polyarthritis at the age of 16 followed by questionable cardiac involvement. He had previously been admitted to another institution where blood cultures revealed *Str. viridans* and penicillin therapy had been instituted, 100,000 units daily for 10 days. There had been a temporary response, but after cessation of therapy, symptoms recurred and blood cultures were again positive. On Oct. 22, 1944 he was admitted to the Presbyterian Hospital with malaise and fever of four weeks' duration. Physical examination revealed fever, mitral and aortic rheumatic heart disease, palpable spleen and petechiae on the finger tips. Four blood cultures were positive for *Str. viridans*, and the organism was one-eighth to one-sixteenth as sensitive to penicillin as the standard strain. Penicillin therapy was started on November 1, 500,000 units daily by intramuscular drip and continued for 10 days. The temperature response was prompt; blood culture became sterile on the third day and remained so throughout the period of treatment. Although the patient continued to be asymptomatic, a blood culture taken four days after cessation of therapy was again positive and shortly thereafter there was a recrudescence of fever. Blood cultures remained positive in the two succeeding weeks and on November 30 penicillin was resumed. Five hundred thousand units were again given daily by intramuscular drip and therapy was continued for 10 days. Throughout this period, the temperature remained normal but the day following discontinuation of treatment, it rose to 103° F. and the blood culture was again positive. Although in vitro tests showed that there was no significant change in the penicillin sensitivity of the infecting strain, the evidence strongly suggested that the infection could not be terminated by the dosage of penicillin which was then available. The patient was therefore placed on maintenance doses of sulfadiazine and allowed to return home for Christmas. In the meantime, a supply of penicillin permitting more intensive therapy became available. The patient was accordingly readmitted on December 29 and immediately started on 1,000,000 units daily by continuous intramuscular drip. Heparin was not employed. Therapy was continued for 14 days. The blood culture was sterile on the fifth day and remained so thereafter. During the first week the temperature remained below 100° F. but rose to 103° F. during the second week and on the fourteenth day reached 105° F. However, there were no associated symptoms and it was concluded that the febrile response was due to local irritation from the intramuscular drip. When therapy was discontinued, the temperature promptly fell and the erythrocyte sedimentation rate gradually returned to normal; blood cultures remained sterile and the patient continued to be asymptomatic. He was discharged on February 6 apparently in excellent health. At the time of the last follow-up visit seven months after cessation of therapy, the blood culture was sterile and there was no evidence of a recurrence of the infection. He has since returned to full time office work, looking the picture of health.

*Case 28.* J. G., a man aged 28, known to have had several attacks of rheumatic fever and chorea in childhood, was admitted on Dec. 1, 1944 with fever, loss of weight and energy in the preceding two and a half months. Examination revealed mitral and aortic valvular disease, palpable spleen, conjunctival petechiae and temperature of 101–104° F. Four blood cultures yielded *Str. viridans*, one-quarter as sensitive to penicillin as the standard strain. Penicillin was started on December 13, 500,000 units daily by constant intramuscular drip, and continued for 10 days. Heparin was not employed. Except for a rise to 101.8° F. on one occasion the temperature remained normal throughout. Blood cultures at the termination of therapy and at weekly intervals thereafter were sterile. The patient gained 10 pounds (4.5

kg.) in weight while in the hospital and the erythrocyte sedimentation rate gradually fell to normal. He was discharged on Jan. 11, 1945 feeling extremely fit. Since then he has been working full time as an accountant and regular follow-up examinations have shown no evidence of a recurrence of the infection.

*Case 29.* H. B., a man aged 51, had had low-grade fever, fatigue, migratory pains, weight loss and malaise since April 1944. There was no history of rheumatic fever or heart disease. He had continued to work as a bookkeeper until October 27 when he was suddenly seized with severe substernal pain and admitted to the hospital two hours later. Examination revealed classic signs of anterior myocardial infarction and he was placed on the usual coronary regimen for four weeks. During this period the white blood cell count returned to normal, but the temperature and erythrocyte sedimentation rate remained elevated and he continued to feel ill. There was a systolic murmur at the apex, the spleen was palpable and the fingers clubbed. During the sixth week embolic phenomena were observed on the left middle finger and in the fundus of the right eye. Blood cultures, which had hitherto been reported sterile, revealed an indifferent streptococcus on four occasions. The organism was one-half as sensitive to penicillin as the standard strain. On December 29 penicillin was started, 500,000 units daily by intramuscular drip, and continued for 10 days. During the first week of therapy, there was a favorable response in temperature and great subjective improvement. During the last three days a recrudescence of fever occurred which was interpreted as a reaction to the intramuscular penicillin. Throughout the period of treatment the patient continued to have drenching night sweats, the erythrocyte sedimentation rate remained rapid, the white blood cell count was slightly elevated, and he passed several small emboli to the upper extremities. In spite of these ominous signs, therapy was discontinued on the tenth day. In the following three weeks he continued to improve and to gain weight; the temperature gradually returned to normal, night sweats ceased, the erythrocyte sedimentation rate fell from 115 to 45 mm. in one hour and five blood cultures were sterile. He was discharged on Feb. 2, 1945, three and a half weeks after cessation of therapy, in good general condition. The patient has now returned to his work and is in excellent health. Blood cultures taken at monthly intervals have all been sterile.

Comment: The patient continued to pass emboli and had fever, leukocytosis and a rapid erythrocyte sedimentation rate after the infection had apparently been controlled. Similar observations have been noted in several other patients.

*Case 30.* M. M., a youth aged 16, had been followed in the Pediatrics Cardiac Clinic since the age of 6 because of congenital heart disease, thought to be due either to an interventricular septal defect or patent ductus arteriosus. The past history included a transient cerebral episode with hemiplegia at the age of 6, bronchitis and bronchial asthma at the age of 12 and primary atypical pneumonia at 14. In June 1943 he was admitted to the hospital with malaise, fever and night sweats. There was a loud harsh systolic murmur with thrill over the mid-sternum. No petechiae were observed and the spleen was not palpable. For 10 weeks he continued to run an irregular fever which responded temporarily on two occasions to sulfadiazine. Although blood cultures on eight occasions were reported sterile, the consensus of opinion was that he had subacute bacterial endocarditis and he was discharged on maintenance doses of sulfadiazine. During the following 15 months he continued to run an intermittent fever and had several episodes suggesting pulmonary infarction. The spleen was also palpable. His general condition, however, remained remarkably good and in August 1944 he was readmitted for further study. A non-hemolytic micrococcus was isolated from the blood on two occasions but numerous other cultures were sterile. Blood respiratory gas studies carried out after catheterization of the right heart made the presence of an interventricular septal defect appear unlikely and exploration for patent ductus arteriosus was performed. At operation a patent ductus

could not be demonstrated. The subsequent course of the disease was essentially unchanged. The patient continued to run an intermittent fever with occasional episodes suggesting pulmonary infarcts. Dyspnea on exertion increased but he continued to be up and about. On Jan. 11, 1945 he was readmitted for further study and possible penicillin therapy. A low-grade fever persisted and on four occasions a slow-growing microaerophilic micrococcus was isolated from the blood. The organism was sensitive to penicillin but the exact degree of sensitivity could not be determined with accuracy. Penicillin therapy was started on January 18, 500,000 units daily by intramuscular drip, and continued for 10 days. The subsequent course was uneventful. The temperature remained below 100° F., the erythrocyte sedimentation rate fell from 50 to 5 mm. in one hour and blood cultures were sterile. Therapy was discontinued on January 28 and the patient was discharged on February 8, completely asymptomatic. At the time of the last follow-up visit he continued to look the picture of health and blood cultures remained sterile.

*Case 32.* M. B., a girl aged 13, was admitted Feb. 26, 1945 with the complaint of recurrent chills and fever of five months' duration. A heart murmur had been recognized since infancy and there was no history of rheumatic fever. Symptoms of chills and fever had been present since September 1944 with daily rises in temperature to 103° F. for the past month. During the last 10 days there had been showers of petechiae. Sulfonamides, 2 gm. daily, had been administered on several occasions with but temporary relief of symptoms. Physical examination revealed a temperature of 102.3° F., the appearance of chronic illness, a palpable spleen and several petechiae. The heart was not enlarged, but in the fourth interspace to the right and left of the sternum there was a harsh systolic murmur thought to be due to an interventricular septal defect. Blood cultures on four occasions revealed an indifferent streptococcus which was equally as sensitive to penicillin as the standard strain. Therapy was started on March 5, 200,000 units of penicillin daily by constant intramuscular drip for seven days. Four days after stopping treatment the temperature was normal and blood culture sterile, but in four more days the fever recurred and blood culture was positive. A second course of penicillin, 500,000 units daily for 10 days was started on March 22. The clinical response was again excellent, and serum levels of penicillin averaged 0.2 unit per cubic centimeter. However, nine days after therapy, fever and a positive blood culture reappeared, the organism having the same sensitivity as it had had originally. Accordingly, 14 days after the second course, a third period of treatment was undertaken, this time 1,000,000 units for 14 days. Serum levels of penicillin averaged 0.4 unit per cubic centimeter. Low-grade fever persisted during this course, apparently caused by the intramuscular drip, for the temperature fell to normal 24 hours after cessation of therapy. The blood culture was sterile five days later, but on the ninth and twelfth days, although there were no clinical signs of relapse, growth was again obtained. The organism was still equally as sensitive to penicillin as the standard strain.

Although her clinical condition remained excellent, it was clear that this patient was unusually refractory to treatment. It was therefore decided to try a more prolonged course of therapy. Accordingly, she was given four weeks of continuous intramuscular penicillin, 500,000 units daily starting on May 15. The response to this fourth course appears to have been satisfactory. The patient has had consistently negative blood cultures and has been sent home free from symptoms.

*Case 33.* E. A., a man aged 50, had rheumatic fever in 1919 and a heart murmur thereafter. In August 1944 he noticed fever and weight loss. Blood cultures at another hospital revealed an indifferent streptococcus and he was given penicillin, 20,000 units every two hours intramuscularly for two courses totalling 3,500,000 units each. Blood cultures became negative during therapy, but growth was again obtained one week after each course.

He was admitted to the Presbyterian Hospital on March 24, 1945. Physical examination revealed a chronically ill male with clubbed fingers and a palpable spleen. The heart was enlarged and overactive with loud aortic systolic and diastolic murmurs. Blood cultures revealed an indifferent streptococcus which was one-half as sensitive to penicillin as the standard strain. Penicillin was administered starting on March 26, 500,000 units daily by constant intramuscular drip for 13 days. Blood culture was sterile on the fourth day and eight different cultures taken before his death remained so. On the third day of therapy the patient developed a left total hemiplegia probably due to embolization of the right middle cerebral artery. Following this he ran a downward course, developed cardiac failure, bronchopneumonia and severe cachexia. He died two and a half months after therapy was stopped. At autopsy he was found to have complete rupture of one aortic cusp and several elongated vegetations on the mitral valve. Postmortem heart's blood was sterile in two flasks. Ground up bits of vegetation which had been taken without aseptic technic cultured only *B. subtilis* and gram negative rods. Microscopic sections of the vegetations showed no bacteria.

In this case, although the infection was controlled, the patient died from complications of the disease.

*Summary of Results and Discussion.* Of the 15 additional cases reported, the infection appears to have been terminated in every instance. One patient (Case 21) died suddenly seven months after therapy and at autopsy was found to have no evidence of persisting infection. One patient (Case 32) has relapsed repeatedly but at present appears to be bacteria-free two months after therapy. In one further instance (Case 33) the infection was controlled but the patient died of cardiac failure two and a half months after therapy. Ten of the 15 patients have already returned to full activity.

It is noteworthy that of 11 patients treated for periods of 14 days or less, the infection was terminated in all but one instance. In every case the serum level maintained was at least two to four times the amount necessary to inhibit the organisms by our in vitro test. In some patients the rôle of previous courses of penicillin in the ultimately favorable result is difficult to evaluate. It is possible that partial healing of vegetations had already taken place although complete sterilization had not occurred as a result of previous treatment. However, in 6 cases in which a single course of 10 days' duration was the only penicillin received, the infection appears to have been terminated as judged by follow-up periods varying from six to nine months.

### PART III: AN APPRAISAL OF THE RÔLE OF HEPARIN IN THE TREATMENT OF BACTERIAL ENDOCARDITIS

The use of heparin combined with penicillin in the treatment of bacterial endocarditis has been advocated by Loewe<sup>3</sup> and others. In their previous report the authors<sup>1</sup> have discussed their experiences with heparin in 15 cases and expressed the opinion that it was of doubtful value. The effect of penicillin alone as observed in 12 additional cases reported herein offers further evidence that heparin is not essential in the treatment of this condition. In fact, results with penicillin alone have been if anything slightly

better than with heparin added. Furthermore, it is the authors' impression that fewer embolic phenomena occur when heparin is omitted while the risk of hemorrhage is of course avoided and the treatment greatly simplified.

There are, however, two possible indications for the use of heparin in treating certain cases. First: in some instances in which large emboli have lodged in major vessels, it may be advisable to heparinize the patient in order to prevent retrograde thrombosis in the artery and thus to keep the collateral circulation open. Second: when extremely large doses of penicillin, say 5,000,000 to 10,000,000 units per 24 hours, are employed, thrombophlebitis at the site of intravenous infusion commonly occurs. Heparin may be useful in minimizing this complication of therapy. The authors have, however, successfully administered 10,000,000 units per day\* by constant intravenous drip for as long as 16 consecutive days without employing anticoagulant therapy.

In summary, it is the authors' opinion that the use of heparin in treating bacterial endocarditis is contraindicated except under the specific circumstances mentioned above.

#### PART IV. FOLLOW-UP REPORT ON THE 15 PATIENTS PREVIOUSLY REPORTED

In an earlier paper<sup>1</sup> the authors reported on 15 patients who had apparently recovered from subacute bacterial endocarditis following penicillin therapy. The follow-up periods had varied from 22 months to one month at that time. These patients have now been observed over an additional 10-month period. There has been no evidence of recurrence of the infection in any of the 15 patients, nor has there been any change in their general health. None has died of other causes and none has developed cardiac failure. Repeated blood cultures have been sterile in all of the 15 patients. The follow-up periods in this group now range from 11 months to 32 months with an average of 18 months.

Combining the figures in the two groups reported by the authors we have the following results: of a total of 35 patients, 5 have died of all causes; the remaining 30 patients are all alive and apparently free from infection at the present time. The average period of follow-up for the entire group is 14 months.

#### PART V. TENTATIVE PROPOSALS FOR THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

There is no doubt that penicillin is an agent of unprecedented value in the treatment of this disease. From the results herein reported it seems likely that the great majority of patients in *whom the offending organism is sensitive to penicillin* can be cured of the infection. The optimum regimen for accomplishing this end is not as yet clearly established, the principal

\* This case will be reported in detail elsewhere by one of the authors (T. H. H.)

unanswered questions being: how much penicillin, by what route and for how long?

The answer to the first question, that is the daily dosage should probably be governed primarily by the sensitivity of the organism to penicillin. This is a biological measurement and as such is subject to many inherent inaccuracies. Furthermore, the translation of in vitro results into guides to therapy must necessarily be subject to question. Nevertheless, a rough approximation can be reached. As a working hypothesis it has been found advisable to maintain a serum level of penicillin at least four times as high as that amount required to inhibit the growth of the organism in vitro. This excess is perhaps necessary for penetration to the depths of the vegetations. On the other hand, there is some evidence that the discrepancy between in vitro measurements and levels of penicillin required in the blood may be explained by the different growth characteristics of organisms in broth and in the body.

In choosing the route by which penicillin is to be given, several possibilities must be considered. The oral administration of the drug may eventually become the method of choice. At present, however, there is little information pertaining to serum levels obtained by this method. Furthermore, results appear to vary considerably from patient to patient. The authors have had no experience with this route of administration but intend to investigate it in the future.

Although some patients unquestionably have responded favorably to penicillin given intramuscularly every two or three hours, it would appear desirable to administer the drug in a manner which assures a more uniform serum level. Therefore it is recommended that the constant intramuscular drip be used as the method of choice at present. Doses up to one or two million units per day can be given in this way without undue discomfort. For larger amounts it is advisable to employ the constant intravenous drip.

The most difficult problem in treating this disease is deciding how long to continue therapy. There are no recognized criteria for evaluating the status of the infection while therapy is in progress. One is forced to treat the patient for a given period, and then to discontinue at an arbitrary time. Further observation after stopping penicillin is the only means of judging the results. Fortunately the vast majority of relapses occur within a few days after cessation of therapy. In our experience the longest interval between treatment and relapse has been two weeks. Thus it is possible with a fair degree of certainty to tell within a short time whether or not a given course of therapy has been successful. It has therefore been our practice to start with a course of two or three weeks' duration, to which the majority of patients has responded favorably whenever the penicillin serum level has been adequate. When relapses have occurred, a second course of penicillin has been administered either using a higher daily dose or in rare instances employing the same amount per day over a more extended period of time. On the whole, better results have been obtained by increasing the daily dose

and thereby raising the level of penicillin in the blood, than by giving small amounts of the drug for protracted periods of time. In difficult cases, even though repeated relapses may occur, it cannot be too strongly emphasized that, if the infecting organism is sensitive to penicillin, eventual cure should be achieved barring complications such as cardiac failure or fatal embolic phenomena. There is no justification for abandoning hope of cure even though four or five courses of therapy have proved unsuccessful.

The foregoing recommendations have assumed access to a laboratory where measurements of the organism's sensitivity to penicillin and of penicillin serum levels can be obtained. Under circumstances where such facilities are not readily available, it is suggested that an initial course of 500,000 units per day for two or three weeks be tried. If blood cultures remain positive, or if relapse occurs following cessation of treatment, it is advised that the penicillin sensitivity of the infecting organism be determined at all costs. Otherwise, valuable time may be lost and large amounts of penicillin needlessly wasted in treatment which this information would immediately show to be inadequate or hopeless.

TABLE II  
Correlation of Penicillin Serum Levels with 24 Hour Dose Administered  
by Constant Intramuscular Drip

Daily Dose (units)	Aver. serum level (u/c.c. of serum)	Range of values (u/c.c. of serum)	Number of Determinations
200,000	.07	.03 — .28	19
300,000	.09	.07 — .28	4
500,000	.2	.025 — .8	113
1,000,000	.56	.5 — 6.4	42
2,000,000	1.6 — 2.24	.56 — 4.48	21
5,000,000	3.2	1.6 — 12.8	16
10,000,000	6.66	6.4 — 51.2*	17

Serum levels were determined according to the method described elsewhere.<sup>4</sup>

\* This very high level occurred in a patient with transient azotemia.

The measurement of serum levels of penicillin is not as essential to rational therapy as is knowledge of the sensitivity of the organism. The serum level can be predicted with reasonable accuracy from the daily dose of penicillin. Table 2 shows the levels of penicillin obtained in the serum on various doses of penicillin administered by intramuscular drip. Levels obtained by constant intravenous drip have been entirely comparable with those obtained by the constant intramuscular route in our experience.

#### SUMMARY

Thirty-five cases of subacute bacterial endocarditis have been treated with penicillin. The group includes 15 new cases and a follow-up on 17 of the 20 patients previously reported.

Of the 35 patients, 30 are alive and apparently cured of the infection. The average period of follow-up has been 14 months.

Some patients required very large doses of penicillin, in one case 92,000,000 units in repeated courses, for termination of the infection.

The rôle of heparin as an adjuvant to therapy with penicillin is discussed and the opinion expressed that in most cases its use is inadvisable.

Tentative proposals are advanced for the future treatment of this disease, stressing the importance of giving large daily doses for periods of two or three weeks.

With persistent therapy, it should be possible to cure the disease in the great majority of cases in which the infecting organism is sensitive to penicillin.

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# AMEBIASIS IN MILITARY OVERSEAS RETURNEES\*

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## INTRODUCTION

THERE is no accurate estimate of the incidence of amebiasis in the United States. The results of independent and uncoordinated local surveys have failed to predict an acceptable national figure because of the failure in most instances to utilize accepted criteria for uniform and dependable studies. Despite the incredibly divergent estimates which have been published in recent years, general agreement has tentatively placed the incidence of carriers somewhere between Craig's 10 per cent<sup>1</sup> and Faust's 20 per cent<sup>2</sup> of the total population. Recently Brown, McHardy, and Spellberg<sup>3</sup> have reported 14.1 per cent incidence in a Louisiana survey of ambulatory patients, and have commented, "Amebiasis is a common disease in the South." Other surveys have suggested that it is only a little less common in the North and West as well.

Apprehension has been expressed concerning the possibility that soldiers returning from service abroad may appreciably enlarge the existing domestic reservoir of amebiasis. The well known ubiquity of functional and bacterial diarrheas in all troops has not prevented reports of such symptoms in our overseas soldiers from strengthening this impression. Recent evidences of such anxiety have included the suggestion that all overseas returnees should receive treatment with amebicidal drugs on suspicion alone and without regard for the demonstration of *E. histolytica* in individual cases. The opportunity for a better understanding of the actual situation has been afforded by the availability of a representative group of military returnees from the more important geographical areas, and the facilities and personnel required for a well controlled and standardized survey.

## CLINICAL MATERIAL

This report deals with the first consecutive thousand unselected cases to enter this hospital directly from overseas in 1944. Approximately 40 per cent of the group were returned because of predominantly surgical or orthopedic conditions, while of the 60 per cent who were admitted on the medical service, only about one third were returned because of gastrointestinal diseases. Nearly all were young males, with an average age of 29.6 years. Duration of overseas service ranged from three to 40 months, with an average for all cases of 11.5 months. Residence prior to entry into the military service represented all of the 48 states.

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From the AAF Regional Hospital, Coral Gables, Fla.

## METHOD

A minimum of three stool examinations was made in each case. Specimens were obtained routinely following mild saline purgation, and were usually collected on alternate days, beginning with the day after admission. All specimens were sent to the central laboratory soon after passage, and none was accepted after 11 a.m. to guard against appreciable drying or cooling before the stools reached the examiner. All samples were examined by technicians with adequate special training of six months or more, under the direction of an experienced parasitologist. Each specimen was subjected to three procedures: (1) direct fresh smears, with or without the addition of Lugol's solution, (2) iron-hematoxylin stained smears, and (3) zinc sulphate centrifugal flotation. All positive cases are represented by a fixed stained smear which is filed in the central laboratory.

## INCIDENCE

Chart 1 indicates the geographical areas in which the major portion of the overseas time was served. Many of these individuals served for shorter periods in one or more different locales, and nearly all passed through more than one geographical region en route to their ultimate destination. It is

CHART I

Geographical Area	Number	Positive Cases	Percentage
Temperate:			
England.....	66	10	15.2
North Pacific Alaska.....	7	1	14.2
Total.....	73	11	15.1
Subtropical:			
Mediterranean.....	249	46	18.4
Caribbean.....	71	8	11.2
Total.....	320	54	16.8
Tropical:			
Central and West Africa.....	34	4	11.8
South America.....	90	11	12.2
South Pacific.....	65	10	15.4
China, Burma, India.....	418	78	18.6
Total.....	607	103	17.0
Grand Total.....	1000	168	16.8

obvious that the total number of cases representing some of the areas is too small for the determination of a reasonably accurate incidence. For this reason the larger divisions; temperate, subtropical, and tropical have been included to reduce the margin of unavoidable error resulting from failure to discover *all* of the positive cases. Perhaps the most striking impression gained from these data is the relatively high incidence in those who served exclusively in temperate zones, although it is now well known that amebiasis is endemic in the British Isles as in all other countries.

Chart 2 is included because of the strong likelihood that many of the positive cases existed prior to enlistment in the Army, or at least prior to departure for overseas service. Careful surveys were obviously not possible at the time of induction, but it is not unreasonable to suppose that if such studies had been made the incidence would have approximated or exceeded the findings of Sapero and Johnson<sup>4</sup> who examined Naval recruits and found the incidence 14.7 per cent in the South and 7.8 per cent in the North. The small number representing the Mountain and Pacific Coast states pre-

CHART II

Residence Prior to Military Service	Number	Positive Cases	Percentage
North East.....	307	49	15.9
North Central.....	265	43	16.3
South East.....	225	46	20.4
South Central.....	138	25	18.1
Mountain.....	37	3	8.1
Pacific Coast.....	28	2	7.1
Total.....	1000	168	16.8

North East: New England, N. Y., Pa., N. J., Del., Md., D. C.

North Central: Ohio, Mich., Ind., Ill., Wis., Minn., N. D., S. D., Nebr., Iowa.

South East: W. Va., Va., N. C., S. C., Ga., Fla., Ky., Tenn., Miss., Ala.

South Central: Kans., Mo., Ark., Okla., La., Tex.

Mountain: N. Mex., Ariz., Nev., Colo., Utah, Idaho, Wyo., Mont.

Pacific Coast: Wash., Ore., Calif.

cludes ready acceptance of the apparent lower incidence for this area. The fact that northern states are represented by more than half of the group suggests the need for an upward revision of previously accepted estimates therefrom.

The total incidence for the group, 16.8 per cent, does not represent a figure significantly higher than that of many reported estimates for domestic amebiasis. If this small sample is in any way indicative of what may be expected in subsequent returnees, there is little basis for apprehension regarding post-war increases in this disease. It is, of course, difficult to estimate the danger of the possible introduction of new strains of *E. histolytica* at this time, as Florio<sup>5</sup> suggests. With maintenance of high levels of sanitation and personal hygiene, however, it is unlikely that such eventuality will represent serious danger to the public health.

#### CLASSIFICATION

Although opinion differs regarding relative frequency of occurrence, three main types of amebiasis are recognized. There is little argument about the criteria for acute amebic dysentery, but little or no agreement has been reached in the establishment of a clear symptomatology for chronic amebic dysentery. The predilection of many clinicians for separation of the carrier-state into a symptomatic and an asymptomatic state leads to further

confusion in classification and much overlapping between the chronic dysentery group and the carrier group. Most of the discrepancy regarding relative incidence of the three types has been caused by the all inclusive and sometimes extremely vague symptoms attributed by many to the presence of *E. histolytica* in the bowel. Chart 3 reveals the type of infestation present on admission in the positive group of 168 cases. It is strikingly significant that 76.2 per cent are *totally* asymptomatic carriers despite the well known influence of a strange and often dangerous environment in the creation of a functional gastrointestinal disturbance. Quite certainly, a large number of

CHART III  
Analysis of the 168 Positive Cases

	Acute	Chronic	Carrier State
Number of Cases.....	6	34	128
Percentage of Total Positive Cases.....	3.6%	20.2%	76.2%
Trophozoites only.....	3	13	32
Cysts only.....	1	16	76
Trophozoites and Cysts.....	2	5	20
Examined by Proctoscope.....	6	30	96
Ulceration Noted on Proctoscopy.....	5	6	3
Percentage With Demonstrable Ulceration	83.0%	20.0%	3.1

the 20.2 per cent classified as chronic amebic dysentery actually belong in the carrier group, and could be so classified were it not for the coexistence of a functional diarrhea or symptoms of irritable colon. Most of these became asymptomatic after appropriate treatment for amebiasis, but one must not overlook the salutary effect of returning home upon functional symptoms created primarily by overseas service.

Many in this group, as well as most of those in the acute amebic dysentery group, had received early and vigorous treatment with amebicidal drugs in overseas hospitals prior to their return. Without question this is the explanation of the very low incidence of both dysenteric amebiasis and the extraintestinal complications of amebiasis in returnees. Although occasional cases of amebic hepatitis and amebic hepatic abscess have been returned, the number has been small and there were none in this group of one thousand.

### DISCUSSION

The epidemiological significance of the *E. histolytica* carrier depends to a great extent on the degree to which the organism can be considered essentially saprophytic or at least harmlessly parasitic, in the same manner as certain strains of *E. coli*, *E. nana*, and a host of other protozoan bowel inhabitants. Faust<sup>6</sup> has suggested that certain cases may demonstrate a minimal amount of superficial mucosal disease, but suggests further that there is very likely no such condition as a perfect balance between host tissue

and parasite. Many of the non-pathogenic protozoa, particularly certain of the flagellates, have been very suggestive causative agents in abdominal disturbances, including diarrhea states, where lowered intestinal mucosal resistance has been caused by one mechanism or another. In a similar manner the *E. histolytica* carrier-state may be converted to acute or chronic amebic dysentery. The rôle of bacillary dysentery in effecting this change has been suggested by Horster,<sup>7</sup> and the nutritional deficiencies developed by many soldiers stationed in remote areas could also be a major factor in such conversion. All of the positive cases have been treated intensively

CHART IV

Coexistent Protozoa	Acute	Chronic	Carrier State
<i>E. coli</i> .....	2	3	24
<i>E. nana</i> .....	1	7	30
<i>Giardia lamblia</i> .....	0	3	9
<i>Dientameba fragilis</i> .....	0	1	1
<i>Trichomonas hominis</i> .....	0	1	3
<i>Chilomastix mesnili</i> .....	0	1	2
<i>Iodameba butschlii</i> .....	0	0	1
Total cases demonstrating one or more co-existent parasites.....	3	8	42
Percentage infested with coexistent protozoan parasites.....	50.0%	23.4%	32.9%

with the simultaneous administration of carbarsone and one of the iodo-hydroxyquinolines, usually chiniofon or diodoquin.

It is of some interest to note the coexistence of other protozoan parasites in the *E. histolytica* positive group, as indicated in chart 4.

#### SUMMARY

1. In 1000 consecutive unselected military returnees from overseas service, *E. histolytica* was demonstrated in 168 or 16.8 per cent.

2. The highest incidence occurred in individuals who had served in tropical areas overseas, and in those who resided in Southern States prior to enlistment in the Army.

3. Of the positive cases, 76.2 per cent represented the asymptomatic carrier-state, 20.2 per cent chronic amebic dysentery, and 3.6 per cent acute amebic dysentery.

4. Prompt and intensive treatment of all proved and suspected cases in overseas hospitals explains the low incidence of dysenteric amebiasis and amebiasis complications.

5. The incidence herein reported is not significantly higher than that reported by many surveys conducted in the United States.

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# TSUTSUGAMUSHI FEVER: AGGLUTINATION REACTIONS AND CLINICAL OBSERVATIONS IN 25 CASES \*

By IRVING GREENFIELD, Captain, M.C., F.A.C.P.

RICKETTSIAL diseases have been known to man for over a thousand years.<sup>1</sup> With the advent of World War II, a large concentration of our armed forces has been on active duty in the regions of the globe where rickettsial diseases are endemic. One of these rickettsial diseases, epidemic or Old World typhus, has been the subject of concern in the past. As the result, considerable knowledge concerning it has been accumulated.<sup>2</sup>

Tsutsugamushi fever, one of the other rickettsial diseases, is an acute febrile disease transmitted to man by the bite of the larval stage<sup>3</sup> of the kedani mite. Clinically, it resembles the other rickettsial diseases. Information concerning this specific disease is comparatively scant. It was deemed of value, therefore, to publish this report in order to make as many observations as possible available for future studies.

*Synonyms.* The variety of descriptive terms employed to identify this particular rickettsial disease referred to the mite borne disease as it occurs in the endemic areas of southern Asia, and the islands of the Southwest Pacific. Thus, one finds that Japanese River fever, kedani fever, Japanese flood fever, tsutsugamushi fever, scrub typhus fever, Mossman's fever of North Queensland and pseudo-typhus of Sumatra have been used to indicate the same clinical disease.

*Etiology.* The etiological agent was described in 1920 by Hayashi.<sup>4</sup> Ogata<sup>5</sup> subsequently confirmed the observations which linked *R. tsutsugamushi* etiologically to Tsutsugamushi fever. *R. niponica*, *R. orientalis*, and *R. tsutsugamushi* were names used in different communications to indicate the agent etiologically responsible for this infection. Immunological studies on rabbits and monkeys were performed by Lewthwaite and Savoor<sup>6</sup> who established the fact that tsutsugamushi fever of Japan and scrub typhus of the Federated Malaya States were identical. Since these diseases were shown to be immunologically identical, it follows that they have identical etiological agents.

*Reservoir.* There is evidence to suggest that the disease is readily transmitted to white mice and other rodents. It is transmitted from these reservoirs to man by the bite of the larval form<sup>3</sup> of a mite *Trombicula acarina*.<sup>7</sup>

*Epidemiology.* The group of 25 cases reported in this communication occurred in a small coastal area of New Guinea in the foothills of the Owen Stanley mountains where the annual rainfall is between 200-300 inches. The greater part of the rainfall occurs between May and August. Kunai

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grass, approximately three to four feet in height, is abundant. Dense jungle, mud, and a thick underbrush add to the conditions so favorable to the natural habitat of rodents and for the development of the mite. Infection occurred among troops who were assigned to work details which cleared areas of Kunai grass, and were either on maneuvers or on bivouac in the jungle. Since all of the cases occurred in military personnel, the age group was a young one. Three were in their late teens. Two were in the 30-40 year bracket. The remainder were in the 20-30 year group. One of the patients was a female who spent an afternoon on authorized recreation in an area where the Kunai grass had not been cut.

*Incubation Period.* We were unable to determine the date of inoculation. However, all of the patients were on duty in areas where conditions suitable for growth and development of larvae existed. Lippman and his co-workers<sup>8</sup> estimated that an incubation period of less than two weeks was common. The only known exposure in one of the patients reported in this communication was an assignment to a detail which cleared an area of kunai grass one week before his hospitalization. On admission he complained of malaise, aches and pains in his joints, and fever. He had a fully developed eschar on the perineum. The incubation period in this particular case was no more than four days. Another patient ran a low grade fever for a period of two weeks prior to admission. During this time he also had three chills. His course was hectic for five days during which his temperature fluctuated between 101° and 105° F. The titer of the Weil-Felix reaction, which on admission was negative in a dilution of 1:20, rose to positive in a dilution of 1:40 on the sixth hospital day when his temperature dropped sharply. Another patient complained of loss of appetite and malaise for four days prior to admission. During this period he had two chills. He, too, ran an extremely toxic course, with delirium, pulse irregularity, abdominal distention, and feeble heart tones. His systolic blood pressure, in mm. of mercury, dropped from 130 mm. to 90 mm., and the diastolic pressure dropped from 90 mm. to 50 mm. Neither of the latter patients had an eschar. Blood drawn from these patients on the day following the initial break in the fever demonstrated a rising titer of agglutination. The incubation period in these three cases varied from four days to two weeks. Prodromal symptoms which consisted of malaise, headache, chills, fever, loss of appetite and varying degrees of weakness together with multiple pains and aches were present in all of the patients for a period which varied from four days to two weeks prior to their admission to the hospital.

*Symptoms.* Most of the patients were admitted with a diagnosis of fever of undetermined origin and since blood smears which were taken routinely to rule out malaria were negative, we were able to obtain a clear and uncomplicated picture. The symptoms noted on admission are listed in the order of their frequency in chart 1. Headache, weakness, and fever were complained of by all. The headache varied in type and severity. It was described as aching, pounding, splitting or blinding. The weakness, as



described, varied from a slightly increased ease of fatigability to almost complete exhaustion. Backache and loss of appetite were next in the order of frequency. Of the group of 16 who complained of pains in the joints, two were admitted to the orthopedic service with a diagnosis of lumbosacral strain. The presence of an eschar suggested the diagnosis which was subsequently proved by a rising titer of agglutination. Two complained of a cough which was dry, hacking and non-productive. Neither had evidence on physical examination or on roentgenographic study to indicate parenchymal lung disease. Hyperesthesia, an uncommon complaint, was considerably troublesome in one patient with a most severe headache. Universal cutaneous hyperesthesia was so marked that the patient could not tolerate the weight of the bed sheets. One of the patients who complained of stiffness of the neck had sufficient nuchal rigidity to indicate a lumbar puncture. Examination of the spinal fluid revealed no abnormalities other than a slightly increased manometric pressure.

CHART I  
Symptoms in Order of Frequency

Symptoms	Incidence
Headache.....	25
Loss of appetite.....	25
Fever.....	25
Malaise.....	20
Backache.....	20
Soreness of muscles.....	17
Soreness in joints.....	16
Chills.....	25
Frequency of urination.....	3
Stiffness of neck.....	3
Hyperesthesia.....	3
Cough.....	2
Fatigue.....	3

*Physical Examination.* The findings on physical examination lend themselves to division into two general groups: those which were present on admission, and those which developed during the course of the disease. The paucity of physical findings on admission was amazing. The patients were usually acutely ill, yet they presented very few positive features. Among the more typical findings were those present in the skin. The most characteristic of these was a small necrotic ulcer which may be present anywhere on the body. It occurred at the site of the mite bite, was usually 2-5 mm. in diameter, and had a black necrotic center which was surrounded by a red areola. It may also be present as a raised, indurated lesion with a yellowish apex. Removal of the skin at the apex of the lesion usually exposed the crater of the underlying ulcer. Characteristically, the eschar did not suppurate. It was painless and frequently remained unnoticed unless it was on an obviously exposed area. Eschars were present in 80 per cent of the cases herein reported. They were located on the perineum, axilla, the lower extremities, scalp, and breast. They were present in 72 per cent of Lippman's<sup>8</sup> cases and in 32 per cent of those reported by Ahlm and Lipshutz.<sup>9</sup>

Two of the patients were admitted with the rash in the early phases of its eruption. It consisted of a rose colored maculo-hemorrhagic lesion. The erythema which was deepest in the center of the macule faded out toward the periphery. The lesion measured 3-5 mm. in diameter, was discrete, did not fade on gentle pressure and showed no tendency toward coalescence. A hectic malar flush of the type seen in acute exanthematous diseases in children was present in four cases.

Lymphadenopathy was the next most common positive finding. Regional lymphadenopathy was present in all of the patients who had an eschar and in some who did not have them. One patient was admitted with a diagnosis of lymphadenitis, acute, non-suppurative, non-venereal of undetermined origin. Aside from the malaise, lassitude, slight headache, and elevated temperature, his only positive finding was two enlarged, tender, post-cervical glands which were about the size of an unshelled peanut. A rise in the agglutination titer established the diagnosis. Far more commonly, though, the regional lymph nodes draining the eschar were enlarged, tender and painful. The glands were discrete, firm, freely movable and tender. Universal lymphadenopathy was present in four patients. Multiple chains of enlarged glands were not uncommon. The spleen was found enlarged on admission in eight cases. It presented all of the characteristics of an acute infectious splenomegaly. Its size varied from one which was palpable at the costal margin to one palpable  $1\frac{1}{2}$  fingers'-breadth below the border of the last rib.

Next in the order of frequency were the ocular findings. Moderately severe conjunctivitis was present in 14 patients (56 per cent). Thirteen of the patients (52 per cent) complained of pain on performing extraocular movements and preferred not to use the ocular muscles because of the discomfort which resulted. Eight (32 per cent) had moderately severe photophobia. One patient had a small subconjunctival hemorrhage.

Two patients had a dry, hacking cough with a moderate pharyngitis. In both cases examination of the lung, clinically and roentgenographically failed to reveal any abnormality.

*Clinical Course.* By the seventh day of the disease, the rash had erupted in 88 per cent of the cases. It varied in intensity, usually made its appearance on the thorax first, and then spread to involve the abdomen, shoulders, neck and arms. One patient had a few lesions on his face. The eruptive phase once started required about 48 hours for its completion. The lesion lasted about four days and then faded. In several instances, residual light brown blotches of pigment remained at the site of the lesions for as long as eight days. There was no correlation between the severity of the clinical course and the intensity, phase of development, or duration of the rash.

Lymphadenopathy was present at some time during the course of the disease in all of the cases. The glands remained tender for three to five days. Splenomegaly was present on admission in eight cases and developed subsequently in three additional cases. One was associated with a peri-

splenitis. This patient complained of pain in the left lower chest which cut his breath short, was sticking in character, and was aggravated by deep breathing. No friction rub was audible. A bedside film revealed no abnormalities of the pleura or the lower lobe of the left lung. In the majority of cases, the spleen remained enlarged and slightly tender for three or four days and then returned to normal. Because of marked abdominal distention it was not possible to determine the duration of the splenomegaly in some of the acutely ill cases.

All of the patients ran a febrile course. There was no type of temperature curve which could have been considered characteristic. Some were remittent and were associated with daily chills recurring for two to five days. Others were maintained on an even plateau, between 104°–105° F., for several days. Very few ran a low grade fever. The average duration of fever was 11.3 days, the extremes being three and 20 days. Defervescence by crisis occurred in nine toxic cases. It occurred after five to seven days of a sustained type of fever. During this period the patients were acutely ill. In the remainder, the temperature fell by lysis. In this latter group were several severely toxic and acutely ill patients. In the recovery phase, the initial defervescence whether by crisis or by lysis was often followed by a secondary rise in the temperature, lasting from one to three days.

As a rule, the pulse rate remained slow and out of all proportions to the elevation of the temperature. A pulse rate of 80 or 90 a minute when the temperature was elevated to 103° or 104° F. was the rule. Early in the course of the disease, a dicrotic pulse was not uncommon. In the toxic cases the onset of myocardial involvement indicated by a rise in the pulse rate occurred between the fifth and seventh day. Gallop rhythm, ventricular premature contractions and an indeterminate type of arrhythmia were noted. A tic tac type of embryocardia with a sudden rise in the pulse rate above 120 beats per minute was present in three of the critically ill patients. The precordial impulse which on admission had been visible, palpable, forceful, and localized became diffuse. The cardiac dullness was widened to percussion. The heart tones were distant and indistinct. A soft, short, localized, apical systolic murmur was audible. Cyanosis of the lips and nail beds without evidence of pulmonary congestion was present. These findings were of short duration and subsided following defervescence.

Symptoms referable to the nervous system were interesting. Insomnia was the rule. Retroorbital and frontal headaches were present universally. They were severe and in several cases lasted throughout the duration of the pyrexia. In spite of the hyperpyrexia and in spite of the fact that they appeared acutely ill, most of the patients were pleasant and coöperative. Some were mildly euphoric for several days during which there were no complaints. However, after five or six days of persistent fever, sweats, and headaches, the euphoria gave way to apprehension. An attitude of complete satisfaction and coöperation was replaced by one of indifference

and negativism. Two patients resented being disturbed for therapy and nursing care. Muscular twichings were present in two cases. Neither showed evidence of impaired renal function or had nitrogen retention. Irritability and restlessness were evident. Four patients were extremely irritable and two were delirious for several days preceding the defervescence. Two patients developed a peripheral neuritis. One involved both peroneal nerves; the other involved the right brachial plexus. Both made a complete recovery after a prolonged period of hospitalization.

Pharyngitis developed during the course of the disease in 10 patients. All of them had a nonproductive cough. Four developed an intractable cough which was exhausting, kept them awake at night, and added to their discomfort. Bedside films revealed evidence of increased peribronchial and hilar markings. The findings were consistent with a roentgenographic diagnosis of bronchitis. One patient developed consolidation of the right base on the tenth day of the disease. A clinical diagnosis, which was confirmed roentgenographically, of pneumonia involving the right lower lobe was made. In addition, the right costophrenic sinus was obliterated. There was no pleural effusion. Though the pneumonitis was considered a complication of the disease, it was felt that the adhesive pleuritis was the residuum of pneumonia which had been contracted in childhood.

A moderate degree of dehydration was evident in many of the cases. The tongue was coated and dry. It resembled a strawberry tongue in that its edges and tip were acutely congested. Profuse perspiration was noted in three patients. Weight loss which ranged from 15 to 62 pounds occurred in every case. The outstanding feature of the disease was the profound prostration which was noted in all of the cases.

Abdominal distention was marked in three of the cases. It occurred between the fifth and seventh days of the disease and lasted four, five and six days respectively. In two cases it was so marked as to add to the pulmonary embarrassment already present. In one case it was severe enough to suggest a paralytic ileus. Constipation which responded to mild catharsis was the rule. None of the patients had diarrhea.

The course of the disease was such that the cases could easily be divided into three groups, mild, moderate, and severe. The mild and moderately ill patients presented no major problems and ran what might be regarded as an uneventful course. The severely ill patients ran an unpredictable course and with the onset of defervescence, a dramatic change occurred. Within the space of a few hours, a markedly toxic, severely distended, dyspneic, cyanotic, irrational, and often delirious patient awakened from sleep with a smile on his face, drenched with perspiration, and volunteered the information that he felt better. From that point, convalescence although prolonged because of profound weakness and exhaustion, was uninterrupted. The average duration of the hospital stay for the entire group was 41.7 days with extremes varying between 20 and 91 days.

*Laboratory Data.* There was no alteration in the red cell count or the hemoglobin. The white cell count did not differ markedly from that which was observed in the average patient admitted to the general medical service of any hospital in this area. A mild leukopenia of four to six thousand cells was the rule. Five patients had a white cell count below four thousand. With the onset of complications, one a reactivation of a quiescent pyelitis, another a complicating pneumonitis and three cases of bronchitis, a rise in the white cell count up to 12,000 with a polymorphonuclear leukocytosis was observed. With the exception of the patient who developed recurrent pyelitis, no pathological elements were found in the routine admission or subsequent urinalyses. The exception was a 22 year old soldier who gave a history of having had pyelitis in childhood. He was very vague as to the circumstances surrounding his initial infection but stated that on two or three occasions, following an upper respiratory infection, urinalyses revealed the presence of pus cells. The admission urine specimen contained red cells, clumps of white cells, granular casts, and albumin. A leukocytosis of 9,300 cells with 80 per cent polymorphonuclear leukocytes was present. Blood chemistry revealed normal urea, total protein, and albumin-globulin ratio. A rising titer of the Weil-Felix agglutination reaction supported the diagnosis of typhus fever.

The observations made in this study are in complete accord with those who stated<sup>9, 10</sup> that there was no correlation between the height of the agglutination titer or the rapidity with which it rose and the clinical course. Neither could any relationship between the presence or absence of the eschar and the Weil-Felix reaction be established. Some observations in regard to the Weil-Felix reaction merit attention. In order to facilitate matters the reader is referred to chart 2. Columns 1, 2, and 3 are self-explanatory. In column 4 is recorded the day of the disease on which the OXK titer of agglutination reached its peak. Column 5 records the highest dilution of the agglutination titer. Column 6 shows the day on which the peak of the agglutination titer was reached in relation to the day on which defervescence started. The last column records the duration of the positive reaction.

One must regard the Weil-Felix reaction in the same light as one does the Wassermann test. Typhus fever, therefore, cannot be excluded from the differential diagnosis because of a persistently negative agglutination reaction.<sup>11</sup> The reaction is of value when it is positive in dilutions of 1:160 or when one can demonstrate a rising titer of OXK agglutinins in specimens of blood taken at intervals of several days. The former group is of diagnostic significance, whereas the latter may be accepted as presumptive evidence in favor of the diagnosis. Positive reactions were obtained in 21 cases (84 per cent). The dilutions were sufficiently high in eight of the cases to be considered diagnostic. In the interval between the fourth and the thirteenth days of the illness a rise in agglutination titer was demonstrated in the remaining 13 patients. The Weil-Felix reaction remained negative in four cases.

Agglutinins for OXK in a dilution of one to 40 (1:40) or over were present in the first specimen of blood examined in four of the cases. Two of these showed a subsequent rise in the titer. One, taken on the sixth day of hospitalization or on the day on which defervescence started, contained OXK agglutinins in a dilution of 1:160. In the other case the specimen of blood was taken on the thirteenth day of the disease or when viewed from the temperature chart on the day following the start of the defervescence. OXK agglutinins were present in a dilution of 1:640. The Weil-Felix test was not repeated in the remaining two cases.

CHART II

Case No.	Day of dis. 1st W-F Re- action was taken	Result	Day of dis. OXK titer reached peak	Dil. in which OXK was positive	Rel. bet. height of pos. titer and deferv.	Follow-up WF Reaction
1	2	Neg.	5	1:80	+1 da.	N 8th day
2	3	Neg.	7	1:40	+1 da.	N 2nd day
3	12	Neg.		Neg.	+5 da.	
4	5	Neg.	11	1:80	+2 da.	N 14th day
5	3	1:40	6	1:160	0	N 7th day
6	2	Neg.	7	1:40	-1 da.	N 8th day
7	8	Neg.		Neg.	+3 da.	
8	7	Neg.		Neg.	-3 da.	
9	6	Neg.	15	1:320	0	
10	9	1:80	9	1:80	+1 da.	N 2nd day
11	3	Neg.	10	1:1280	+1 da.	P 14th day
12	6	1:40	13	1:640	+1 da.	P 10th day
13	8	1:640	8	1:640	+1 da.	
14	1	Neg.	11	1:160	+1 da.	
15	7	1:80	7	1:80	-5	N 14th day
16	4	1:40	4	1:40	-3	N 8th day
17	7	1:160	7	1:160	+1	
18	2	Neg.	13	1:160	+1	N 6th day
19	10	Neg.	17	1:320	0	P 3rd day
20	4	Neg.		Neg.	-6	
21	3	Neg.	9	1:80	+1	N 2nd day
22	1	Neg.	12	1:40	0	N 3rd day
23	5	Neg.	8	1:80	0	N 3rd day
24	2	Neg.	10	1:40	+1	N 4th day
25	2	Neg.	7	1:80	+1	N 4th day

A rise in the agglutinin titer was demonstrated in 17 cases. Of these, eight reached dilutions of over 1:160. The remaining nine cases demonstrated a rise in titer in the lower dilutions (i.e., 1:40 or 1:80). Engrafting the date on which the agglutination titer reached its peak on the temperature chart, it was observed that a close relationship existed between that day and the day on which defervescence started. Since the duration of the pyrexia is variable, it is not possible to predict the date on which defervescence will start. However, by watching the temperature curve carefully, it may be possible to select the time at which it would be reasonable to expect that the Weil-Felix reaction would be positive in the higher dilutions. In this small series of cases that period of time which elapsed between the day preceding and the day following defervescence appeared to be optimal. The

series is too small to permit any definite conclusions to be drawn, but the observation was sufficiently striking to warrant further study. It is known that the reaction becomes positive some time during the second week of the disease. The observation cited simply narrows this period down to the time of defervescence. Those reactions which were positive in the high dilutions 1:320 or over, remained positive for upward of a week. Those which were positive in the dilutions below 1:160 had a tendency to fall within a period of two to four days after it had reached its peak. There were four cases in which the agglutination reaction remained negative. The first patient had an eschar on her right breast, enlarged, tender glands in the right axilla, ran a low grade type of fever, and developed a rash on the sixth day of hospitalization. Defervescence occurred on the seventh day. The blood for the Weil-Felix reaction was not drawn until the twelfth day or five days after defervescence had occurred. The second was admitted with photophobia, a rash on his chest, and an eschar on the left tibia situated approximately two inches above the internal malleolus. Defervescence started on the sixth day when the temperature dropped from 104° to 101° F. It then took two days for the temperature to reach the base line. Blood for the Weil-Felix reaction was drawn on the ninth hospital day or three days after the initial break in the fever. Case three had an eschar on the dorsum of the right foot, a universal lymphadenopathy, and a typical rash. He was extremely toxic during the last four days of his fever which was of the remittent type and lasted 10 days with daily fluctuations ranging between 102° and 105° F. Blood drawn on the sixth day of the disease or three days before the start of defervescence contained no agglutinins in a dilution of 1:20. No subsequent examinations were made. The fourth had an eschar on the scrotum, axillary and inguinal lymphadenopathy, a typical rash, and a remittent type of fever for 11 days. Defervescence occurred on the twelfth day of the disease. He ran a moderately severe course. Specimens of blood drawn the fifth and eighth days of the disease contained no agglutinins. Additional specimens were not submitted. In the light of the observations reported in this communication it is suggested that the agglutination reaction might have shown a rising titer had the specimens been taken at the time of defervescence.

*Pathology.* None of the cases studied in this series died. A discussion of the pathology of typhus fever is, therefore, beyond the scope of this communication. However, the reader is referred to an excellent article by Corbett<sup>12</sup> who found that the primary lesion was a diffuse vasculitis and perivasculitis. Some of his cases exhibited a tendency toward thrombus formation.

*Therapy.* In the absence of any specific type of therapy, the importance of complete rest and adequate nursing care cannot be overestimated. Since the treatment is purely symptomatic, the desire to keep the patient comfortable will often constitute a challenge to the therapeutic skill and resource-

fulness of the physician. Its objective should be to allay fear and apprehension and to maintain adequate nutrition. Barbiturates, hypnotics, and narcotics were often necessary to control the headache, insomnia, and restlessness. Acetylsalicylic acid in small repeated doses was often of value in relieving the headache. Frequent sponges are indicated when the fever reaches its peak. The use of an ice cap will occasionally be comforting. In view of the sustained hyperpyrexia supplementary vitamin therapy is of considerable importance. To combat dehydration, the fluid intake was maintained at between three and four liters a day. However, due caution was exercised to avoid overloading an already injured cardiovascular system. Small amounts, one to two units, of plasma were given daily in the severely toxic cases. Whole blood transfusions and a high protein diet when oral feeding is possible seem to be of value. Fruit juices were given freely except in those cases where abdominal distention was a disturbing factor. A variety of enemata, Murphy and Harris drips, rectal tube, pitressin, etc., were employed at various times to alleviate the abdominal distention. Marked prostration often makes colonic irrigation a hazardous procedure, so that one hesitates to use it. Oxygen was given empirically for the relief of dyspnea without demonstrable effect. However, five patients who received oxygen noticed that the headache was relieved. The use of cardiac depressants should be avoided. Cardiac, vascular, and pulmonary complications should be treated promptly as they arise. From the above it becomes evident that standardization of the treatment is not possible.

### SUMMARY

Twenty-five cases of scrub typhus fever observed in an area in the Southwest Pacific were studied. The observations reported in this communication were made from a careful study of the clinical course. The symptoms noted were those reported by the patients. The observations in regard to the physical findings were those which were noted in the record. The behavior of the Weil-Felix reaction was a matter of particular interest. Though the series is too small to permit of any definite conclusions, it suggests that a time might be selected in terms of one or two days when the peak of the agglutination titer might be predictable. The importance of this observation, if borne out by future study, cannot be overestimated in view of the fact that the laboratory facilities in military installations are often taxed to the limit of their capacity. The fleeting character of the positive agglutination reaction in the low titers may offer an explanation for the high percentage of negative reactions reported in some communications. It may also account for the four persistently negative reactions observed in this series.

Agglutination tests were made at the Fifth Medical Laboratory.



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## ASIATIC RELAPSING FEVER; REPORT OF 134 CASES TREATED WITH MAPHARSEN \*

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THIS report comprises 134 cases of relapsing fever of the Asiatic type. Relapsing fever is a spirochetal infection characterized by one or more attacks of fever beginning and ending abruptly and separated by an afebrile period of varying duration.

The disease is prevalent in many parts of the world and assumes the form of a virulent epidemic in famine stricken, debilitated populations. The causative organism is a spirochete of the genus *Spirochaeta* (*Borrelia*) and transmission is by infected lice or ticks. The spirochetes of relapsing fever have been separated by agglutination and other reactions into two groups—*S. recurrentis* (louse-borne), and *S. duttoni* (tick-borne).<sup>1</sup> There has been, in the past, a tendency to subdivide these two groups into various strains on a serological basis, but it is now generally held that differences in the organism are so slight that this is impracticable and sub-division is unnecessary.<sup>2</sup>

The spirochetes enter the body through abraded skin by contamination with crushed material from infected lice. Apparently, the bite of the louse alone does not transmit the spirochete. Though no special studies were made positively to identify the species of spirochete found in the cases presented, the evidence pointed to the louse-borne *S. recurrentis*. Almost every patient had stigmata of recent lice infestation. Information received from the camp in China from which they came was that a large percentage of their population was heavily infested with lice. Clinically, the marked tendency to collapse following a crisis is characteristic of the louse-borne type of relapsing fever. Moreover, no ticks were found on the patients and none gave a history of being bitten by ticks.

*Material.* The conditions surrounding these cases are important. All were admitted between December, 1943 and August, 1944, the majority being seen in May, June, and July, 1944. All were Chinese soldiers and all were treated in a U. S. Army Station Hospital situated in a remote section of Assam, India.

The Chinese were recruits who, fresh from coolie life in China, were flown over the Himalaya "Hump" into Assam. The majority had been in India less than one week before developing relapsing fever and a considerable number were ill at the time of making the flight. Delousing was done in both the Chinese and Indian camps. As the incubation period of relapsing fever is about seven to 12 days, it is probable that most of our cases contracted the disease in China.

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The air route over the Himalayas is one of the most hazardous in the world and is made at altitudes in the neighborhood of 20,000 feet. At such heights, these men were exposed to sub-zero temperatures and oxygen-poor atmosphere. There is no question but that the flight, under these circumstances, played a considerable part in lowering the general resistance of the individual. The Indian camp was located some distance from the hospital, and cases were transported by U. S. Army ambulance. Because of the distance to be traveled and because these troops arrived from China in large numbers, admission of Chinese to the hospital was usually in groups of 20 to 30. Inasmuch as supplies, personnel, and equipment were scarce during the time they were seen, it was impossible to make a detailed study of each case.

As a group, these patients were in exceedingly poor condition. Almost without exception, there were signs of malnutrition and multiple vitamin deficiencies. Many had frank beriberi, a large number had pellagra, and a few had scurvy. Almost 100 per cent of the stools examined contained ova, usually hookworm or *Ascaris lumbricoides*. Though blood counts were by no means routine, enough were done to give a fair index of the group. A hypochromic anemia was the rule, and in no instance was the erythrocyte count within normal limits. Many patients gave histories of typhus fever and repeated attacks of malaria in the past.

The Chinese soldier is in many ways an almost ideal patient, for he is fearless, willing and obedient within the limits of his understanding. However, the average Chinese soldier, particularly the recruit, has no conception of illness comparable to that of the American. Bed rest is almost impossible to enforce. Most of our patients would remain in bed only at the height of their fever or during a particularly severe chill. At other times, they would wander about the ward and frequently take possession of another bed. This led to confusion in identity and mistakes in medication. This was corrected by marking each patient's forehead with his chart number. These, and other similar factors, are of considerable importance in treating a large number of patients of foreign tongues and ways.

Histories were obtained through interpreters and at best, contained only the essential facts. No attempt was made to obtain more than a sketchy past history. In many instances, it was discovered that two interpreters gave entirely different histories on the same patient. This may be partly explained by the serious condition of the patients, but in general, the histories were unreliable. This was of particular importance when treatment was considered, as the duration of the febrile attack in relapsing fever is one of the determining factors in the institution of specific therapy. A few patients who succumbed, probably died because of inaccurate timing of treatment. This disturbing factor was partly overcome by the medical officers and nurses learning sufficient spoken Chinese to obtain a more reliable history.

Upon admission to the hospital, all patients were given a shower bath, and a search was made for lice. Only a very few were found to be harboring lice or nits.

Immediately on being put to bed, thick and thin blood smears were taken. These were stained with Giemsa stain and examined under oil immersion. A few fresh, wet preparations were made on the early cases, but as the volume increased, it became impracticable to use this method. Smears were repeated at frequent intervals until reported positive or until relapsing fever had been ruled out. Spirochetes were, in most cases, found on the first smear and were usually plentiful. Many smears showed tremendous numbers of organisms in each field, most often occurring in clumps of 10 or more. The number of spirochetes found on blood smears served as a rough guide to the severity of the infection. However, some of the critically ill patients showed only a few spirochetes and, rarely, a patient would show large numbers of the organisms with only mild clinical findings. All positive smears were checked by trained workers. Only those cases with *S. recurrentis* found in the blood smear are included in this series.

TABLE I  
Clinical Summary of 134 Cases

Symptoms on Admission	No. of Cases
Fever.....	119
Muscular aching.....	116
Cough.....	85
Chills.....	64
Weakness.....	54
Constipation.....	51
Diarrhea.....	41
Dizziness.....	38
Physical Findings	No. of Cases
Transient râles.....	70
Splenomegaly.....	59
Muscle tenderness.....	52
Hepatomegaly.....	22
Jaundice.....	15
Conjunctivitis.....	11
Rash.....	7
Deafness.....	6

*Clinical.* (A summary of the clinical findings is seen in table 1.) On admission, the patients usually presented one of two striking clinical pictures. The more common was that of the febrile attack. The complaints were dizziness, fever, cough, headache and muscular pains. The temperature was of the sustained type, usually above 104° F., with the pulse rapid and full. Dehydration was marked with dry, hot skin and flushed, anxious facies. The conjunctivae were frequently injected. Wheezing râles and rhonchi with rapid, shallow respirations were common findings. The spleen and, less often, the liver were apt to be enlarged and tender. Tenderness in the calf muscles was a characteristic finding. This stage was abruptly terminated a few hours after the administration of an arsenical. However, there were many cases on whom treatment was withheld and the attack was allowed to run its course. It was found that the initial attack lasted from five to 15 days, whereas subsequent attacks were of much shorter duration,

rarely lasting longer than five days. The febrile attack in both instances ended in an abrupt crisis.

The second type of patient was that admitted in profound circulatory collapse following the crisis. Practically all of these men were in a critical condition and required immediate supportive treatment. The main complaints were thirst and marked weakness, particularly in the legs. The skin was cold and clammy in spite of evident dehydration. An ashen pallor was present. Apathy was marked. The temperature was usually below normal and the pulse was rapid and thready. Diarrhea was common in this stage. Splenomegaly was almost invariably present.

The length of the circulatory collapse varied considerably with individual cases, but in general, it rarely existed longer than 12 hours. In that time, the patient either recovered or succumbed.

*Diagnosis.* The clinical diagnosis of relapsing fever in a tropical zone is difficult. It must be differentiated from malaria, typhus, rat-bite fever, dengue, pappataci fever, and a host of other acute febrile conditions.

The frequency of respiratory symptoms and signs, notably those of bronchitis, is a clue to relapsing fever. The pulse is usually more rapid than in most tropical fevers. Weakness and prostration are pronounced and, coupled with pain and tenderness in the calves of the legs, are suggestive of relapsing fever. A polymorphonuclear leukocytosis is often, though not invariably, present.

The only certain means of diagnosis is through the detection of the organism in the blood smear. In this series, spirochetes were found in all stages of the disease but, as would be expected, were far more numerous during the febrile attack.

*Treatment.* Uncomplicated relapsing fever usually responds dramatically to intravenous arsenicals. Only one or two injections are required to effect a cure. In the past, epidemics have been reported in which salvarsan and neoarsphenamine were used with satisfactory results.<sup>3</sup>

In evaluating results from various drugs, the condition of the patients must be taken into account. The economic status of the patient plays a large rôle in the severity of the disease as the mortality rate in epidemics varies inversely with the nutritional state. As stated above, nearly every patient in the group from which these cases were taken was suffering from malnutrition and helminthiasis, and was therefore, in poor general physical condition. However, there were gradations in the severity of the reaction to relapsing fever and, for the purpose of tabulation, cases were classified as "good," "fair," or "poor," according to the estimated condition of each on admission (table 2): Those cases listed as in "good" condition were those who were in a remission and had few or no complaints or physical findings. Those listed as "fair" had only mild complaints and did not appear acutely ill. The majority of these patients were either in the early stages of the febrile attack or recovering from the crisis. Those admitted

TABLE II  
Summary of Treatment and Results

Case Number	Condition on Admission	Marpharsen			Number of Days from Admission to Defer- vance	Out- come	Number of Days from Admission to Death	Remarks
		Number of Injections	Dosage in Grams	Interval in Days Between Injections				
1	Fair	1	0.06		14	R*		Toxic reaction to mapharsen
2	Fair	1	0.06		12	R		Toxic reaction to mapharsen
3	Poor	1	0.06			D†	2	Died in circulatory collapse
4	Fair	1	0.06		2	R		Toxic reaction to mapharsen—parotitis
5	Poor	2	0.06	5	6	R		Recurrence—toxic reaction
6	Poor	2	0.06	2	4	R		Recurrence—toxic reaction
7	Fair	2	0.06	12	15	R		Recurrence—toxic reaction—parotitis
8	Poor	2	0.06	10	12	R		Toxic reaction to mapharsen—recurrence
9	Poor	2	0.06	5	6	R		Toxic reaction to mapharsen—recurrence
10	Poor	2	0.06	5	7	R		Toxic reaction to mapharsen—recurrence
11	Poor	2	0.06	7	8	R		Toxic reaction to mapharsen—recurrence
12	Poor	1	0.04			D	2	Died in circulatory collapse
13	Fair	1	0.04			D	2	Died from severe epistaxis
14	Poor	1	0.06		2	R		Toxic reaction to mapharsen
15	Poor	1	0.04			D	4	Died in circulatory collapse, hemorrhage from bowel
16	Poor	1	0.04			D	1	Died in coma
17	Good	1	0.06		2	R		Toxic reaction to mapharsen
18	Fair	1	0.04		2	R		Conjunctivitis
19	Poor	1	0.04		2	R		Conjunctivitis
20	Poor	2	0.04	3		D	7	Died in coma with hepatitis, rash
21	Good	1	0.04		2	R		Prompt recovery
22	Poor	1	0.04		2	R		Prompt recovery
23	Poor	1	0.04		3	R		Prompt recovery
24	Poor	1	0.04		20	R		Severe epistaxis—parotitis
25	Poor	1	0.04		2	R		Conjunctivitis—rash
26	Good	1	0.04		2	R		Prompt recovery
27	Poor	1	0.04		22	R		Hepatitis
28	Poor	1	0.04		2	R		Rash
29	Poor	1	0.04		3	R		Prompt recovery
30	Poor	1	0.04		14	R		Hepatitis—rash
31	Poor	1	0.04		2	R		Prompt recovery
32	Poor	1	0.04		3	R		Prompt recovery
33	Poor	1	0.04		2	R		Prompt recovery
34	Poor	1	0.04		2	R		Prompt recovery
35	Poor	1	0.04		7	R		Mild epistaxis, prompt recovery
36	Poor	1	0.04		3	R		Orchitis—prompt recovery
37	Fair	1	0.04		3	R		Prompt recovery
38	Poor	1	0.04			D	1	Died in circulatory collapse
39	Good	1	0.04			D	1	Died of convulsions and hyperpyrexia
40	Poor	1	0.04		14	R		Mild epistaxis, prompt recovery
41	Poor	1	0.04		2	R		Prompt recovery

\* Recovered.

† Died.

TABLE II—*Continued*

Case Number	Condition on Admission	Marpharsen			Number of Days from Admission to Defer- vance	Out- come	Number of Days from Admission to Death	Remarks
		Number of Injections	Dosage in Grams	Interval in Days Between Injections				
42	Fair	1	0.04		2	R		Prompt recovery
43	Poor	1	0.04		2	R		Prompt recovery
44	Poor	2	0.04	5	6	R		Recurrence, prompt recovery
			0.04					
45	Poor	2	0.04	5	7	R		Recurrence—mild epistaxis
			0.04					
46	Poor	1	0.04		10	R		Prompt recovery
47	Poor	1	0.04		15	R		Hepatitis—conjunctivitis
48	Poor	1	0.04		6	R		Rash—prompt recovery
49	Poor	2	0.02	3		D	6	Recurrent case, died with circulatory collapse
			0.04					
50	Poor	2	0.04	4	7	R		Recurrence—prompt recovery
			0.04					
51	Poor	2	0.04	3	12	R		Recurrence—hemoptysis, bowel hemorrhage
			0.04					
52	Poor	2	0.04	3	4	R		Recurrence—conjunctivitis
			0.04					
53	Poor	1	0.04			D		Died in coma
54	Fair	2	0.04	2	5	R		Recurrent case—conjunctivitis
			0.04					
55	Poor	1	0.04			D	1	Died of convulsions and hyperpyrexia
56	Poor	1	0.04			D	2	Died of bowel hemorrhage—hepatitis
57	Good	2	0.04	5	6	R		Recurrent case
			0.04					
58	Poor	2	0.04	3	4	R		Recurrent—rash
			0.04					
59	Poor	2	0.04	4	16	R		Recurrence—hepatitis, conjunctivitis
			0.04					
60	Poor	2	0.04	5	6	R		Recurrent case
			0.04					
61	Poor	2	0.04	4	5	R		Recurrent case
			0.04					
62	Poor	1	0.04			D	2	Died of circulatory collapse
63	Fair	2	0.04	3	4	R		Prompt recovery
			0.04					
64	Poor	2	0.04	3	5	R		Parotitis—conjunctivitis
			0.04					
65	Poor	2	0.04	4	5	R		Conjunctivitis—prompt recovery
			0.04					
66	Poor	2	0.04	3	4	R		Prompt recovery
			0.04					
67	Poor	2	0.04	3	4	R		Orchitis, prompt recovery
			0.04					
68	Poor	2	0.04	3	6	R		Parotitis
			0.04					
69	Fair	2	0.04	3	25	R		Mild epistaxis
			0.04					
70	Good	2	0.04	3	2	R		Hepatitis
			0.04					
71	Good	2	0.04	3	4	R		Hepatitis
			0.04					
72	Good	2	0.04	3	8	R		Prompt recovery
			0.04					
73	Fair	2	0.04	3	42	R		Hepatitis, hematuria, bowel hemorrhage
			0.04					

TABLE II—*Continued*

Case Number	Condition on Admission	Marpharsen			Number of Days from Admission to Defervescence	Outcome	Number of Days from Admission to Death	Remarks
		Number of Injections	Dosage in Grams	Interval in Days Between Injections				
74	Poor	2	0.04	3	2	R		Prompt recovery
75	Poor	2	0.04	3	4	R		Prompt recovery
76	Poor	2	0.04	3	2	R		Prompt recovery
77	Poor	2	0.04	4	2	R		Prompt recovery
78	Poor	2	0.04	3	3	R		Prompt recovery
79	Poor	2	0.04	5	14	R		Hemoptysis
80	Poor	2	0.04	3	2	R		Prompt recovery
81	Poor	2	0.04	3	2	R		Prompt recovery
82	Poor	2	0.04	3	2	R		Prompt recovery
83	Poor	2	0.04	3	2	R		Prompt recovery
84	Poor	3	0.04	3 and 10	21	R		Recurrent case, parotitis
85	Poor	2	0.04	3	4	R		Prompt recovery
86	Poor	2	0.04	3	2	R		Prompt recovery
87	Poor	2	0.04	3	2	R		Prompt recovery
88	Poor	2	0.04	3	2	R		Prompt recovery
89	Fair	2	0.04	3	*			*Afebrile on admission
90	Poor	2	0.04	3	1	R		Prompt recovery
91	Poor	2	0.04	3	6	R		Prompt recovery
92	Fair	2	0.04	3	*	R		*Afebrile on admission
93	Fair	2	0.04	3	*	R		*Afebrile on admission
94	Poor	1	0.02			D	1	Died in circulatory collapse—small hemorrhage from bowel
95	Poor	2	0.04	3	4	R		Prompt recovery
96	Poor	2	0.04	3	1	R		Prompt recovery
97	Poor	2	0.04	3	5	R		Prompt recovery
98	Poor	2	0.04	4	5	R		Prompt recovery
99	Poor	2	0.04	3	3	R		Prompt recovery
100	Fair	2	0.04	3	2	R		Prompt recovery



TABLE II—*Continued*

Case Number	Condition on Admission	Marpharsen			Number of Days from Admission to Defervescence	Outcome	Number of Days from Admission to Death	Remarks
		Number of Injections	Dosage in Grams	Interval in Days Between Injections				
101	Poor	2	0.04	3	5	R		Conjunctivitis—prompt recovery
102	Poor	2	0.04	3		D	5	Died of secondary parotitis—small hemorrhage from bowel
103	Poor	2	0.04	5	3	R		Prompt recovery
104	Poor	2	0.04	4	2	R		Prompt recovery
105	Poor	2	0.04	3	2	R		Prompt recovery
106	Poor	2	0.04	3	5	R		Myelitis
107	Poor	2	0.04	3	2	R		Prompt recovery
108	Fair	2	0.04	3	2	R		Prompt recovery
109	Poor	2	0.04	3	4	R		Hepatitis
110	Poor	2	0.04	5	2	R		Prompt recovery
111	Poor	2	0.04	3	2	R		Prompt recovery
112	Poor	2	0.04	3	6	R		Hepatitis
113	Poor	2	0.04	3	6	R		Prompt recovery
114	Poor	2	0.04	3	7	R		Prompt recovery
115	Poor	2	0.04	3	12	R		Hemoptysis
116	Poor	2	0.04	3	9	R		Hepatitis, parotitis
117	Poor	2	0.04	3	5	R		Prompt recovery
118	Poor	2	0.04	3	7	R		Prompt recovery
119	Fair	2	0.04	3	1	R		Prompt recovery
120	Fair	2	0.04	3	2	R		Prompt recovery
121	Poor	2	0.04	3	2	R		Prompt recovery
122	Poor	2	0.04	3	3	R		Prompt recovery
123	Poor	2	0.04	3	4	R		Prompt recovery
124	Good	2	0.04	3	*	R		*Afebrile on admission
125	Fair	2	0.04	3	2	R		Prompt recovery
126	Poor	2	0.04	3	5	R		Hepatitis
127	Poor	2	0.04	3	5	R		Hepatitis

TABLE II—Continued

Case Number	Condition on Admission	Mapharsen			Number of Days from Admission to Defervescence	Outcome	Number of Days from Admission to Death	Remarks
		Number of Injections	Dosage in Grams	Interval in Days Between Injections				
128	Poor	2	0.04	3	2	R		Prompt recovery
129	Poor	2	0.04	3	5	R		Myelitis
130	Poor	2	0.04	3	1	R		Prompt recovery
131	Poor	2	0.04	3	6	R		Conjunctivitis
132	Poor	2	0.04	3	26	R		Hepatitis
133	Poor	2	0.04	3	5	R		Prompt recovery
134	Poor	2	0.04	3	2	R		Prompt recovery

acutely ill, at the height of the febrile attack or during the stage of collapse, were listed as "poor."

Mapharsen (Meta-amino-para-hydroxy-phenylarsine-oxide-hydrochloride) was chosen in treating these cases because of its availability, its known low toxicity, and because of its ease of administration. So far as could be determined, no cases have been reported in which mapharsen was used in the treatment of relapsing fever.

At the outset of the epidemic, all cases received a single injection of 0.06 gram, but because of toxic reactions, this amount was reduced to 0.04 gram. Although one injection of 0.04 gram was often sufficient to effect a cure, the number of recurrences of the disease soon led to the routine use of two injections each of 0.04 gram, given three to five days apart.

In table 2 it is shown that frequently a second injection of mapharsen was given even though defervescence had already occurred. This was done to prevent recurrence. For example, case 90 was admitted with a history of fever, generalized aching and weakness of two days' duration. *S. recurrentis* were found on the first blood smear and, on the day of admission, the first dose of mapharsen was given. The following day the patient was up and about the ward area, afebrile and with no complaints other than weakness. In spite of an apparent cure at this time, a second injection of mapharsen was given on the fourth hospital day. He was discharged as cured on the twelfth hospital day. Nineteen cases (13 per cent) had a recurrence after two injections. The average recurrence occurred on the fifth day, but some were observed as soon as two, and as late as 12 days after the initial injection. The recurrence was in every way similar to the original

attack. However, spirochetes were rarely found on smears taken during a recurrence.

Spontaneous recovery in relapsing fever is known to occur but none was seen by us. Several patients were admitted with no complaints but with a history of a febrile episode just prior to admission. Four of these (cases 89, 92, 93 and 124) had smears positive for *S. recurrentis* on admission. Undoubtedly these patients were in a remission. Mapharsen was given and no further evidences of relapsing fever developed in any case. Other afebrile patients with suggestive histories failed to show spirochetes as long as they were afebrile. Most of these developed attacks within a few days and *S. recurrentis* were then found (cases 69, 70, 71 and 126). In each case mapharsen was given on the first day of fever and resulted in a prompt cure.

In about four hours following the initial injection, most patients developed increased pyrexia of 1 to 2° F. This was often accompanied by a chill and marked generalized aching. This phenomenon was interpreted as representing a reaction induced by the destruction of large numbers of spirochetes with the liberation of toxins and foreign protein. The pyrexia continued for several hours and generally terminated in an abrupt crisis. This was followed by a subnormal temperature and varying degrees of circulatory collapse. In an effort to minimize this reaction a few patients were given 0.04 gram of mapharsen dissolved in 1,000 cubic centimeters of physiologic saline. This was discontinued when results were found to be the same as when the mapharsen was given in only 10 cubic centimeters of solution.

Probably the most important factor in treating relapsing fever is the timing of the arsenical injection. It is generally agreed that the most opportune time is at the beginning of the attack, that is, within two days of the onset of fever. Experience in these cases was in accord with this dictum. It was soon learned that injections given near the time of the crisis invariably resulted in profound changes regardless of the dose of the drug. In some cases, an extreme pyrexia, 108° F. and above, followed the injection. This was usually accompanied by terminal convulsions. The more common reaction consisted of a transient rise in fever followed by deep medical shock which frequently progressed to death in spite of all treatment. In general, it was found that the nearer the arsenical was given to the crisis, the more severe the reaction.

Several patients were admitted in a critical condition even though, according to the history, they had been ill only one or two days. Most of these patients had an extreme pyrexia, 106° F. and above, but a few were in a state of circulatory collapse. Mapharsen given to these patients invariably made them worse. After this lesson was learned, mapharsen was withheld until the subsidence of the attack and was administered at the beginning of the next attack, at which time it could be more safely given. Treatment of these patients during the critical period was entirely supportive.

The treatment of patients in circulatory collapse was the same regard-

less of whether it appeared following mapharsen or in the natural course of the disease. Intravenous plasma, saline and glucose solutions were given along with local heat and stimulants such as caffeine. In spite of intensive supportive therapy the response was usually slow and the majority of these patients died following a progressive pulmonary edema.

Twelve cases (9 per cent) gave evidences of mild toxic reactions to mapharsen. A toxic reaction was thought to have occurred in those patients who developed symptoms and signs not present prior to the injection. There were four instances of mild nausea and vomiting, four of a profuse diarrhea, and four instances where nausea, vomiting, and diarrhea were present. All of these reactions occurred following the first injection of 0.06 gram of mapharsen. With the reduction to 0.04 gram of mapharsen, no further toxic reactions were noted. In addition to the cases mentioned above, there were four patients who had violent chills and fever immediately following the injection. Though these cases might be included in the group of toxic reactions, it was not possible to determine whether this was an attack induced by the destruction of large numbers of spirochetes or a toxic reaction to mapharsen. Because of the absence of nausea and diarrhea, it was felt that an induced attack was more likely.

*Results of Treatment.* All of the 134 patients received one or more injections of mapharsen.

Under ordinary circumstances, a disease such as relapsing fever supplies the ideal medium for measuring the efficacy of specific treatment. Results can be measured in terms of complete recovery or death. However, the presence of other factors such as the nutritional state, concomitant diseases, and a heavy incidence of past diseases will alter, to a considerable extent, the final results. These factors, plus a certain degree of inexperience on the part of those handling these cases, undoubtedly contributed to the mortality rate in this epidemic.

Mapharsen proved to be a very effective drug against relapsing fever. In the entire series, only in two cases were spirochetes found after its use. Both of these cases had tremendous numbers of the organism in the initial smear and both were in a critical condition. In spite of this, a second injection resulted in a prompt recovery in both instances. Toxic reactions were infrequent and were of no consequence in the outcome of any case.

The use of multiple doses of 0.04 gram of mapharsen given three to five days apart was found to be the best method of treatment. Using this plan, the recurrence rate was reduced to practically nil, and toxic reactions were not observed.

In general, convalescence was rapid following mapharsen. In a few days, recovery was complete. Because of the crowded conditions of the hospital, most cases were returned to duty somewhat sooner than was desired, but even in the short period of their hospital stay, a remarkable change was usually seen. The average patient gained several pounds on the solid U. S. Army ration. Routine vermifuges were followed by iron and multi-

vitamin therapy with a visible improvement in vigor and general well-being. One patient, who was retained for duty in the hospital, gained over 30 pounds in six weeks.

*Complications.* The chief complications attributable to relapsing fever were hemorrhage, hepatitis, conjunctivitis, deafness, orchitis, and myelitis. Occurring concomitant with relapsing fever were seven cases of malaria, four of louse-borne (OX-19) typhus, one of smallpox, two of lobar pneumonia, and two of rheumatic heart disease.

Hemorrhage was the most common complication. It was seen in 16 cases (12 per cent). Epistaxis and hemorrhage from the bowel each occurred in six cases, hemoptysis was seen in three patients, and hematuria in one. In two cases, epistaxis was of a serious nature. Both had been bleeding intermittently for two days prior to admission. One succumbed from shock incident to blood loss. The other required tight nasal packing for two days, but made an uneventful recovery. It is likely that these two cases were precipitated by the high altitude flight which they made, as bleeding began during the flight. The remaining four cases of epistaxis occurred during the febrile attacks and were of no consequence.

Hemorrhage from the gastrointestinal tract was present in six cases. In two, it was deemed part of the hemorrhagic diathesis incident to severe jaundice. The other four cases were unexplained. Large amounts of bright red blood were passed in the stools of three cases and tarry stools were found in another. Hemorrhage from the gastrointestinal tract proved to be a bad omen, as four of the six cases were fatal.

The single case of hematuria was seen in an intensely jaundiced individual who also bled from the bowel and had purpuric areas over the extremities. The hematuria was gross and persisted over a period of three weeks. This patient made a slow recovery following mapharsen, vitamin K, and transfusions.

Fifteen cases (11 per cent) of icterus occurred in the series. The jaundice varied from mild to intense and was of the nonobstructive type. Concomitant hepatomegaly was present in all cases and the findings were thought to represent an inflammatory hepatitis produced by the *S. recurrentis*. When present, this complication was usually seen at the time of admission, though two cases developed during convalescence. The disease was fatal in two instances. One patient grew progressively more jaundiced, had profuse hemorrhage from the bowel, and developed purpura of the dependent areas of the entire body. Death followed a short period of coma. The other fatal case also died in coma but did not exhibit any unusual bleeding tendency. The course of the hepatitis was not influenced by mapharsen. It tended to remain for 10 to 20 days with gradual recovery.

A purulent conjunctivitis resembling Koch-Weeks infection was encountered in 11 cases (8 per cent). In two of these, Koch-Weeks bacilli were identified on smear. All cases responded satisfactorily to local sulfonamide therapy. It was not determined if this was a true complication of

relapsing fever or an incidental infection. As conjunctivitis was seen only in the Chinese with relapsing fever, it was interpreted as a true complication.

A rash was found in only six cases (4 per cent). It consisted of a purpuric macular eruption most prominent on the trunk with scattered lesions on the extremities. A concomitant lymphadenopathy was not noted. In each of these cases, typhus was suspected, but was ruled out by agglutination and therapeutic response to mapharsen. The rash remained for four to five days before fading.

The two cases of orchitis appeared suddenly in the form of rapid swelling of the testicle. Both appeared during the febrile paroxysm and both subsided spontaneously within a week.

One of the most interesting complications in the series assumed the form of a mild myelitis in two cases. It was manifested by motor and sensory changes in the lower extremities and was of a very transient nature. The spinal fluids, though clear, showed increased pressure, a positive Pandy test, and a lymphocytic pleocytosis. Spirochetes were not seen in the spinal fluid. No special treatment other than nursing care was required and recovery was complete within three weeks in both cases. It is possible that the marked weakness in the legs seen after the crisis may be on the basis of a low-grade myelitis. Unfortunately, spinal fluid studies were not done on cases other than these two.

Eight patients (6 per cent) developed parotitis. It usually appeared shortly after recovery from the crisis during the period of convalescence. Both glands were involved. On palpation, they were soft and doughy in consistency. No tenderness or other signs of inflammation were present. The openings of Stenson's duct appeared normal and expressed secretions clear. Parotitis was not accompanied by an exacerbation in fever in most cases. It was in no way affected by a second arsenical injection. Parotitis was thought to be a sequel to general debility and poor oral hygiene rather than a true complication of relapsing fever.

Transient deafness was present on admission in six cases. This may well have been an effect of high altitude flying. In no instance did this complication persist and no special treatment was required.

*Fatal Cases.* Previously reported epidemics have given a variation in mortality of from 2 to 50 per cent.<sup>4</sup> Sixteen cases (12 per cent) of the 134 cases in this series, died following treatment with mapharsen. At first glance this figure may seem high, but when the factors mentioned above are considered, it appears, in fact, lower than would be expected. This view is supported by statistics obtained from the Indian camp. A report from that camp stated that 50 per cent of the recruits were ill at the time of arrival from China. The average mortality among recruits hospitalized from whatever cause was slightly above 10 per cent. These figures demonstrate very well the poor condition of the group as a whole.

The cause of death could not be accurately determined because of the

inability to obtain postmortem examinations. Descriptions of the causes of death are, therefore, in clinical terms.

Of the 16 fatal cases, eight died in a state of circulatory collapse, three in coma, two of convulsions and hyperpyrexia, two following severe hemorrhage, and one as a result of a secondary parotitis.

The circulatory collapse appeared shortly after the termination of the febrile attack and proved very refractory to treatment. It strongly resembled the so-called secondary shock.

#### SUMMARY AND CONCLUSIONS

1. The clinical findings and complications in 134 cases of Asiatic relapsing fever due to *S. recurrentis* have been briefly presented and discussed.

2. Mapharsen was administered to all cases and proved to be an effective drug. The best results were obtained when two injections, each 0.04 gram, were given three to five days apart.

3. The mortality of 11.9 per cent was offset by the poor general condition of the patients.

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## CYSTIC DISEASE OF THE LUNG\*

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CYSTIC disease of the lung has long been considered a rather uncommon condition, probably because it rarely gives symptoms and is usually found in the course of routine physical and roentgen examinations. The roentgenograms made routinely at the army induction centers will undoubtedly uncover a great number of hitherto unsuspected cases because these are surely more common than is generally believed.

Recently we had the opportunity to study such a group, many of whom presented the various complications of this disease. Since the literature dealing specifically with the complications of this condition is rather meager, we feel that this report is justified.

No discussions of the cystic diseases of the lung appeared in the American literature until 1925, when Koontz<sup>1</sup> reported a case with an autopsy record and reviewed the foreign literature. Most of the papers since then have dealt with individual case reports and attempts to explain the pathogenesis and pathology of the disease; only since 1935 has any extensive number of cases been reported. The term "cystic disease of the lung" is rather loosely used in the literature. From the examination of many available reports, we feel that cystic disease of the lung may be defined as *any condition in which the lung parenchyma is replaced by sharply defined cavities containing fluid or air*. In order to simplify the discussion we are excluding dermoid cysts of the lung, echinococcus cysts and encapsulated interlobar accumulations of fluid or air. It is generally agreed that cystic lung disease may be congenital, acquired or both, although the prevalent opinion seems to lean to the congenital origin. Both forms have been termed "honey-combed lung" and "cystic bronchiectasis" when the cyst wall contained bronchial components, and "pneumatocele" or "pneumocyst" when the cyst wall resembled bullous emphysema.

From a clinical and pathological point of view, congenital cystic disease falls into two main groups. The first is the large solitary cyst which may occupy one or more lobes, often displacing the heart and mediastinum to the contralateral side. Such cysts compress the surrounding parenchyma and are usually found in infancy and early childhood, giving symptoms of cyanosis and dyspnea, accompanied by physical signs of a tension pneumothorax. These solitary cysts are lined by a layer of columnar and cuboidal epithelium, resting on a tunica propria and a layer of connective tissue. No

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doubt all these cysts communicate with a bronchus, but this communication is very difficult to demonstrate grossly. However, careful serial section of many of these cysts will disclose the communicating bronchus. In the case of Koontz,<sup>1</sup> several communicating bronchi were found in the examination of 50 serial sections. Definite bronchial communication must exist if the cyst is to remain open, since complete bronchial occlusion and failure of ingress of air will cause obliteration of the cyst through the absorption of the trapped air. Cheney and Garland<sup>2</sup> have reported such a congenital cyst in an adult girl 19 years of age, giving the patient no symptoms whatsoever despite the fact that her vital capacity was only 27 per cent of the expected normal. Similar cases have been reported by Wood,<sup>3</sup> Eloesser,<sup>4</sup> Kirklin,<sup>5</sup> Sharpe,<sup>6</sup> and Ford.<sup>7</sup>

The episodes of respiratory difficulty seen in these patients have been ascribed to progressive enlargement of the cysts with the development of positive intraluminary pressure and the displacement and herniation of the mediastinum, or to localized spontaneous pneumothoraces as the cysts rupture under the strain of positive pressure. Soon, however, the rent in the visceral pleura overlying the cyst wall heals and the cyst lumen again enlarges.

Roentgenologically these cysts appear as large areas of radiolucency which may or may not contain fluid. As a rule, the cystic spaces are well defined and are frequently traversed by linear strands of trabeculation. When the cyst cavities are ballooned out by the highly positive intraluminary pressure, the trachea, heart and mediastinum may be displaced into the contralateral hemithorax and a marked resemblance to a tension pneumothorax will be apparent.

The second form of cystic disease which is apparently congenital is one in which the lung parenchyma is replaced by areas of cystic degeneration ranging from multiple miliary cysts scattered throughout lung parenchyma to large multilocular or unilocular cysts occupying one or more lobes. These cystic cavities are lined by cuboidal or columnar epithelium which may be thrown into folds by intraluminary proliferation giving rise to an adenomatous appearance. Between these two extremes intermediate forms may be encountered giving the lung tissue a spongy appearance, it being made up of clusters of thin-walled cavities varying in size from 1 to 3 cm. These cavities communicate freely with bronchi and are lined with columnar ciliated or non-ciliated epithelium and show the usual architecture of a bronchus—smooth muscle, cartilaginous rings and mucous glands being found in the cavity wall on histologic examination.

Radiographically this form of cystic disease is characterized by the honey-combed appearance of the pulmonic fields, the lung structure showing a large number of thin walled, sharply defined annular shadows without accompanying interstitial parenchymal infiltration. This roentgen appearance is especially diagnostic when the lesions are in the upper lobe, are bilateral, and there is no distortion of the thoracic cage or retraction of the mediastinum as seen in the acquired forms of bronchiectasis. However, when infection

is superimposed on a congenital lesion it may be difficult to distinguish from the acquired form by roentgen examination. The direct communication with the bronchus as indicated above can be demonstrated on bronchography and the grape-like clusters of cystic spaces will be found to stand out.

Acquired pneumatocele or cystic disease is usually associated with respiratory infection, chronic bronchitis or peribronchitis, pulmonary fibrosis and emphysema, or bronchial asthma. It is evident that any pathologic lesion



FIG. 1. *Case 1.* Fluid filled cyst. Note round, sharply defined density distinct from mediastinal structures. This shadow represents a congenital cyst of the lung which has not extruded its fluid contents and demonstrates a step in the pathogenesis of the disease.

causing incomplete bronchial obstruction will be followed by obstructive emphysema with distention of the corresponding alveolae and thinning with resultant final rupture of the alveolar septa. Bleb and bulla formation is the inevitable result, especially if the stenotic lesion is such that a check-valve mechanism acts at the bronchial orifice.<sup>8, 9, 10</sup> Pathologically, the acquired form of cystic disease is indicated by the presence of coal pigment in the contiguous alveolar walls and by the existence of blebs and bullae at the periphery of the lung. Lesions of this type may be seen even in infancy and childhood and may disappear when the endobronchial lesion heals and, as a matter of fact, cases of this type were reported by Caffrey.<sup>11</sup>

Roentgenographically, acquired pneumatocele presents itself as a poorly defined annular shadow devoid of pulmonary markings. Close scrutiny will show fine linear bands traversing the cystic space. This, too, is to be distinguished from localized pneumothorax. It is obvious, then, that from a roentgen and clinical point of view, it may be very difficult to distinguish the acquired from the congenital form of solitary cyst described above. The fact that most cases of the latter die in infancy and early childhood makes one suspect an acquired etiology when this lesion is seen in an adult. However, Kirklin<sup>5</sup> and Cheney and Garland<sup>2</sup> have described cases in adults who had large solitary cysts with ballooning and herniation of the mediastinum.

Roentgenographically, the differential diagnosis from a localized pneumothorax may be made by the establishment of a diagnostic pneumothorax when the cyst wall will be separated from the thoracic cage and its cystic nature will become discernible. Again, the introduction of a pneumothorax needle into the cyst lumen and the measurement of the intraluminary pressure manometrically before and after the aspiration of a given volume of air, will also help to establish the differential diagnosis. Removal of air will alter intraluminary pressure very little in cystic disease, whereas well defined changes in the intrapleural readings will take place in localized pneumothoraces. As stated earlier, bronchial connections are difficult to demonstrate macroscopically; hence, bronchographic examination will fail to visualize contrast medium in the cyst space. However, compression of the surrounding lung parenchyma will bunch the bronchi in the vicinity of the cyst. Case 12, showing a large pneumatocele, illustrates this point very nicely.

The pathogenesis of congenital cystic disease is very interesting. The most plausible explanation is as follows: It will be remembered that the lungs are formed from the lung buds whose ends become lobulated at about the fourth week of embryonic life, there being three lobules formed on the right and two on the left. These lobules undergo dichotomous branching, the terminal portions of the branches becoming expanded to form atria. At about the sixth month, the alveoli are formed as evaginations from the latter. If the process is arrested early, during the early subdivisions, large solitary cysts may be formed. If the process is arrested later in embryonic development, multiple cysts will result. It will be remembered too, that the thoracic cage grows much faster than its contents. If then no pulmonary alveoli are formed and the development of the bronchopulmonary segment does not keep pace with the increased capacity of the fetal thorax, dilatation of the involved bronchi will follow; case 4 illustrates this point very well. The lateral view shows the huge dilated bronchi with cyst formation.

Another factor which very likely plays a part is the fact that there may be an arrest in the development of the bronchiole in the tube stage. Excretion of mucus from the glandular elements of the bronchiolar wall may form fluid-filled sacs. When the intraluminary pressure rises the sac may rupture

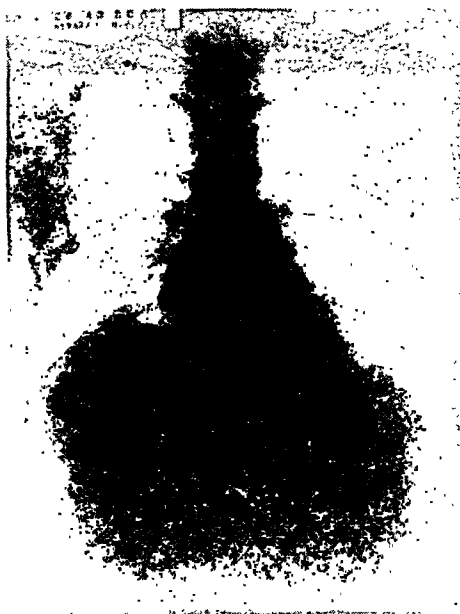


FIG. 2.



FIG. 3.

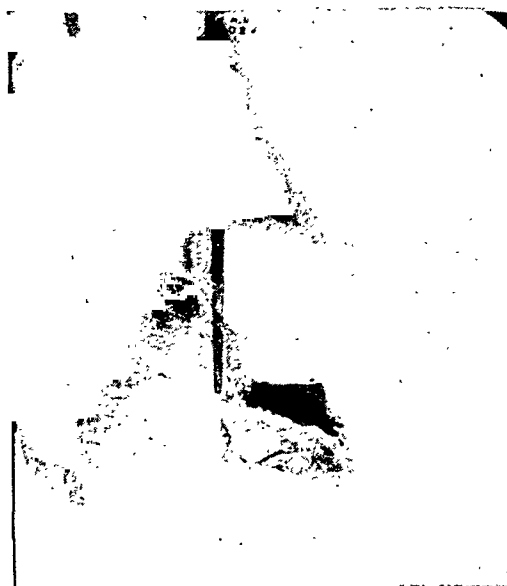


FIG. 4.

FIGS. 2, 3, and 4. *Case 3.* Congenital cystic disease complicated by hemorrhage. Roentgenogram of chest showing area of diminished illumination of right lower lung field and tenting of right diaphragm due to pulmonary fibrosis and pleural thickening from previous pneumonitis and empyema. Frequent episodes of hemoptysis suggested bronchograms, figures 3 and 4, demonstrating large cysts filled with contrast medium.

and its contents empty into a bronchus. Air now enters the cystic space and it in turn dilates, especially if the mechanism at the bronchial orifice is of the check-valve or bi-pass variety. Credence is given to this theory by the presence of fluid-filled pulmonary cysts which never give rise to symptoms and are only discovered as incidental findings during routine roentgen examinations as seen in case 2.

The most plausible theory of the pathogenesis of the acquired form of cystic disease has been discussed above. In addition, it has been suggested by Wolbach<sup>12</sup> and by Rabinowitz and Rogers<sup>13</sup> that vitamin A deficiency may cause the accumulation of keratinized epithelial cells in the bronchial



FIG. 5.



FIG. 6.

FIGS. 5 and 6. Case 7. Cystic disease of the lung complicated by infection. Figure 5 shows bucky exposure of the chest during attack of pneumonitis. Trachea, heart and mediastinum are deviated to the left. Numerous annular shadows can be visualized in the left upper lobe. Figure 6: Under chemotherapy, pneumonitis subsided and thin-walled annular shadows can be visualized above the third anterior rib. Note how difficult it is to distinguish this case from that of the acquired disease.

lumen, causing in turn obstructive emphysema and cyst formation. The diet in all cases observed by us was certainly adequate and it is difficult, therefore, for us to incriminate a vitamin A deficiency.

It is well to keep in mind that cystic disease of the lung (uncomplicated) rarely gives rise to symptoms. Aside from the large solitary cysts which balloon out under the influence of a check-valve mechanism at the bronchial orifice and are fatal early in life, cystic disease seldom gives symptoms. Only after close questioning will the patients divulge the fact that they have had a non-productive cough which is not at all distressing. However, upper respiratory infections are very often followed by infection in the cystic areas and episodes of pneumonia are obtained from many of the histories.

The severe constitutional symptoms associated with acquired bronchiectasis are not seen in these cases; neither are the cerebral manifestations associated with pulmonary suppuration. As age increases and cardiorespiratory reserve diminishes, the patients often complain of increasing dyspnea; in fact, death from right-sided heart failure is not uncommon. Routine physical or roentgenographic examinations usually establish the diagnosis. However, complications of this disease are common and some of these bring the patient to the attention of the doctor. Probably the most frequent of such complications is hemorrhage, occurring in four of our 13 cases. The hemorrhage is seldom profuse, although in case 5 it was of exsanguinating proportions, necessitating repeated transfusions on several occasions. It is, indeed, noteworthy that the literature fails to emphasize hemoptysis as an important symptom; Kirklin<sup>5</sup> even goes so far as to state that it is rare. On the other hand, cases reported by Smith,<sup>14</sup> Hennel,<sup>15</sup> and Churchill<sup>16</sup> presented hemorrhage as the main complaint. The true source of the hemorrhage has not been definitely established. Case 5 had her hemoptysis following febrile episodes associated with pneumonitis in the surrounding lung parenchyma. It seems that infection in the cyst wall eroded a bronchial or pulmonary blood vessel and thus caused the hemorrhage. However, cases 2 and 3 had hemoptyses without antecedent infections. Perhaps blood vessels coursing in the cyst wall, unsupported on their luminary side, are prone to rupture under the strain of increased intrapulmonic arterial pressure.

The next complication in order of frequency is infection with surrounding pneumonitis; this occurred in two cases of our series. In each case the infection ran a protracted course and gave a sulfonamide response. It is worthy of note that in case 6 an attack of pneumonia caused the patient to be examined by a physician and thus the true nature of the underlying condition became apparent.

The third complication encountered in our series was spontaneous pneumothorax. This is clearly brought out in case 9, whose spontaneous pneumothorax complicated congestive heart failure. Only after this complication was truly evaluated and the appropriate therapy instituted was the patient benefited.

Case 8 developed a spontaneous hemopneumothorax as a result of bilateral apical emphysematous bullae which were probably congenital in origin. No evidences of parenchymal fibrosis of tuberculous or any other origin could be found. The rupture of a vascular adhesion secondary to the pneumothorax was probably the origin of the bleeding.

Acquired cystic disease was discovered incidental to examination for food handlers certificates as in case 11, during routine cardiac teleroentgenography in case 10, and while in search for a cause of progressive dyspnea in case 12. Particularly interesting is case 5, in that repeated attempts to demonstrate bronchiectasis by roentgenogram, bronchography and bronchoscopy were unsuccessful. A differential diagnosis from bronchial adenoma had to be

considered. Finally, laminography by H. K. Taylor of New York City demonstrated the true nature of the condition, i.e., cystic disease.

Case 1 is presented to show the pathogenesis of congenital cystic disease. Here a large round density was found in the right lung field during routine periodic health examination. It had been present for at least five years without any increase in size and had caused no symptoms. The patient refused to allow us to aspirate the cyst and we did not press her because we felt that it might be dangerous to do so. Such masses must be distinguished from solid lung tumors, especially teratomata, neurofibromata and carcinomata. The duration of the lesion and its sharply defined outline militate against these diagnoses. Moreover, its radiographic appearance, as a parenchymal density, well circumscribed, slightly less radio-opaque than the opacity of the cardiac shadow, and separated from the latter, fits in well with the diagnosis of cystic disease of the lung.

### CASE REPORTS

#### FLUID FILLED CYSTIC DISEASE

*Case 1.* M. J., a 38 year old colored female, was first seen by one of us in 1940, when a physical examination was made for a health card as a domestic. She had no physical signs and no complaints. During routine fluoroscopic examination a large, sharply defined annular shadow presented itself. Since the patient had no complaints and refused any other diagnostic procedures, no attempt was made to aspirate the mass or remove it. The patient was later seen on two occasions in addition to the original examination; she was apparently perfectly well and the roentgen shadow was essentially unchanged. We believe that this shadow is due to a congenital cyst of the lung which has not extruded its fluid contents.

#### CYSTIC DISEASE COMPLICATED BY HEMORRHAGE

*Case 2.* E. J., a 22 year old colored male, entered the hospital in November, 1942, following hemoptysis of one quart of bright red blood. Past history was negative except for pneumonia at ages of 18 months, seven, nine, and 10 years. At the age of 11, the patient was admitted to Glen Gardner Sanatorium with a diagnosis of chronic pulmonary tuberculosis. He remained there a whole year and was discharged with a diagnosis of lung abscess of the right middle lobe. Physical examination was entirely negative except for the chest which showed dullness and diminished breath sounds in the right middle lobe. Roentgenograms disclosed an annular shadow in the right lower lung field with a dense wall and a fluid level. Lateral view proved this shadow to be in the right middle lobe. Subsequent lipiodol instillation confirmed the contention that this shadow was a large congenital cyst, freely communicating with a bronchus. The patient was advised to have a right middle lobectomy, but refused.

*Case 3.* M. L., a 29 year old white male, was first seen by us on November 13, 1943, complaining of right sided chest pain. The patient had apparently been well until the age of nine, when he had several small hemoptyses of three ounce quantities. At the age of 12 he had an attack of pneumonia complicated by empyema, necessitating several rib resections. The patient was hospitalized at this time for nine months. Even during his hospital stay he had two pulmonary hemorrhages. The patient fared very well thereafter, having only vague pains in his right chest on change of weather.

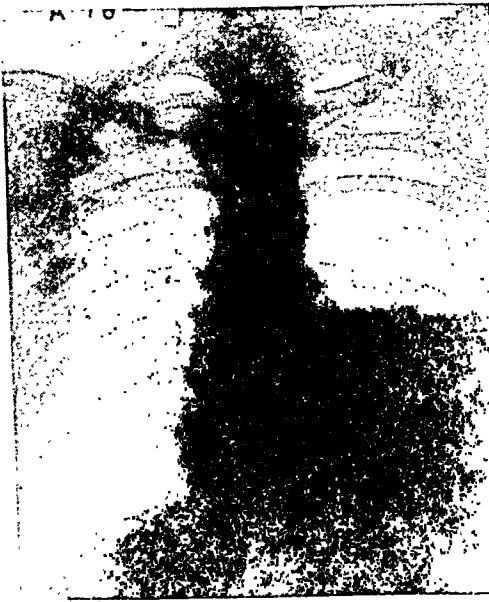


FIG. 7.

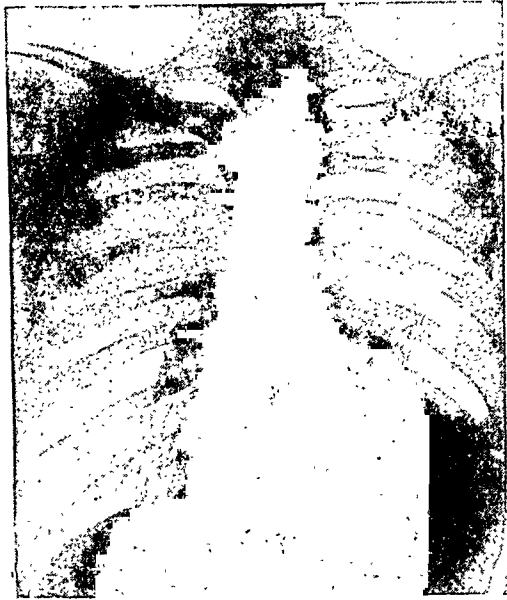


FIG. 8.

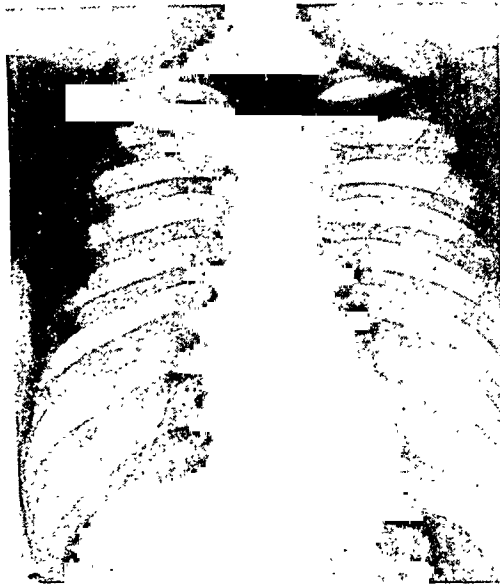


FIG. 9.

FIGS. 7, 8, and 9. *Case 8.* Cystic disease complicated by spontaneous hemopneumothorax. Figure 7 shows left hydropneumothorax with fluid level at the fourth anterior rib. There is some shift of the trachea, heart and mediastinum to the right. Several emphysematous bullae may be visualized at the extreme apex of the right upper lobe. Figure 8: After aspiration and oxygen lavage, the lung reexpanded. Fluid proved to be frank blood which did not coagulate on standing. Figure 9: Lung completely reexpanded, emphysematous bullae may be noted at the extreme apices.



At this time positive physical signs were limited to the chest where dullness and diminished breath sounds were found over the right lower and middle lobes. He was seen periodically and treated symptomatically. In June, 1943, the patient was inducted into the Army and during his basic training another hemoptysis occurred, this time amounting to about one pint. He was hospitalized and finally discharged with a diagnosis of bronchiectasis. He again returned to us for further studies. A lipiodol instillation into the right middle lobe showed a large cystic cavity which occupied the greater part of the right middle lobe and only now the true nature of his disease became evident. Figures 2, 3 and 4 show the ease with which the lipiodol entered this cystic cavity.

*Case 4.* S. G., a 34 year old white female, was first examined by one of our group on March 13, 1945, complaining of ready fatigue and pain in the upper anterior chest for the past two weeks. The patient had been well for eight years prior to this time, when she had a pulmonary hemorrhage of about two ounces. She had no premonitory signs and felt perfectly well for the succeeding two years when she had another hemoptysis. Since then she had repeated bleedings at two year intervals. In the interim there had been no cough, expectoration, chills or fever. The patient never experienced the symptoms of pneumonitis. The last hemoptysis occurred two years prior to this examination. Past history was unimportant with the exception of typhoid fever in 1918. The positive physical signs were limited to the chest; here there was a slightly tympanic percussion note in the left upper lobe with diminished breath sounds and occasional medium moist râles. Roentgen examination showed an area of increased illumination occupying the left upper lobe in which lung markings could be made out only at the periphery. At the level of the anterior third rib, a definite annular shadow could be seen. The cystic bronchiectatic nature of the disease was easily demonstrated on bronchography where the iodized oil flowed into the left upper lobe bronchus, revealing large dilated bronchi and annular cystic cavities. Obviously, the only cure for such a lesion is a left upper lobectomy.

*Case 5.* J. M., a 21 year old female, was seen by us for the first time on July 10, 1944, complaining of cough, fever, and hemoptysis of three days' duration. The patient was well until February 1933, when she developed chills, fever and a cough, productive of a thick greenish yellow mucus. A diagnosis of bronchopneumonia was made at this time and was said to have been corroborated by roentgenographic findings. The patient was ill intermittently with the same chain of symptoms for the next year and a half. She then returned to school, but complained of left-sided pleuritic pain aggravated by coughing on rare occasions. For the next six years she was perfectly well. However, in April, 1939, the patient had a pulmonary hemorrhage amounting to about eight ounces. She remained in bed for about one week during which time she had mild streaking. In July of the same year she had a severe hemoptysis, requiring frequent transfusions; her hemoglobin fell to about 40 per cent. At this time the patient was hospitalized for one month; roentgenograms showed an exudative lesion of the left hilus. Bronchoscopy failed to reveal any endobronchial lesion. This procedure was done for the purpose of eliminating papillary carcinoma or benign adenoma of the bronchus as likely etiologic factors. Bronchogram at this time was unsatisfactory. Finally the hemorrhage ceased; the patient regained her strength and was discharged. In October, 1940, and August, 1941, the patient again developed brisk hemoptyses; both of these followed acute upper respiratory infections with "chest" colds. Each time the patient was laid up for three weeks. In September, 1943, she again had a hemoptysis of four ounces; this followed an attack of chills and fever. At this time the patient came under our observation. Physical examination showed dullness, diminished bronchovesicular breath sounds in the left upper lobe with occasional râles in the left axillary areas above the fifth rib. Roentgenographic examination revealed an area of diminished illumination extending along the inter-

lobar fissure, which was interpreted as an area of pneumonitis or an interlobar effusion. The patient was given sulfonamides with absolutely no therapeutic response. After 10 days her temperature, which had been up to 103° F., came down to 99° F., and she improved subjectively. However, the shadow as noted above remained, finally clearing in about six weeks. Attempts to ascertain the true cause for the hemoptysis were now made; iodized oil instillation failed to reveal any bronchiectasis. Bronchoscopy again was done; no intrinsic disease could be found in the left bronchial tree. Since a small calcified node was seen at the left hilus and it was suggested that this may have eroded a branch bronchus, thus causing the bleeding, a laminography was done to establish whether or not this calcified node bore a definite relation to a bronchus. The patient was referred to Dr. H. K. Taylor of New York City, who took layer films; at the levels of 3¼"-4" from the anterior chest, definite cystic spaces were visualized and the true nature of the disease process was demonstrated.

#### CASES COMPLICATED BY INFECTION

*Case 6.* M. M., a 15 year old white female, was seen by us on September 3, 1942, complaining of cough and expectoration lasting three weeks. The patient was perfectly well until August 16, 1942, when she developed left-sided chest pain and a non-productive cough. Her temperature rose to 103° F., and was preceded by a severe chill. She was taken to Rockaway Beach Hospital, where a diagnosis of bronchopneumonia was made. The patient was given sulfonamides with but indifferent results, the temperature falling by lysis after 10 days. At the time of our observation on September 13, 1942, she felt weak and coughed with profuse expectoration which was mucopurulent, occasionally blood-stained, but always non-fetid. Essential physical findings were limited to the lungs where the percussion note was somewhat diminished over the left upper lobe anteriorly and the breath sounds diminished; an occasional rhonchus was audible over this area. Roentgenographic examination revealed an area of infiltration along the base of the left upper lobe representing an area of pneumonitis and interlobar effusion. In this region several annular shadows could be found, the lowermost of which contained a fluid level. Sputum and gastric contents were negative for acid-fast bacilli after repeated examinations. Culture of the sputum failed to show Friedländer bacilli and was positive for hemolytic streptococcus. The patient was given supportive treatment and improved. Bronchography failed to reveal any contrast substance in the cystic cavities, although the major bronchi draining the areas of the cystic spaces were visualized. The patient was seen on May 23, 1944; the cystic spaces were still apparent. The pneumonitis had completely cleared and the patient had no complaints.

*Case 7.* F. C., a 42 year old white clerk, was first referred to us on November 15, 1944, complaining of cough and expectoration of a non-fetid, mucopurulent sputum. His previous history disclosed four attacks of pneumonia; the first at the age of six, the second at 36, the third at 41, and the fourth at 42. The last one occurred in September, 1944. The patient during the last attack complained of an upper respiratory infection which gradually descended into his chest, as evidenced by chills, fever, left-sided chest pain, and marked increase of cough and expectoration. At this time he was hospitalized and treated with sulfonamides to which he gave a definite chemotherapeutic response. He spent his convalescence in Florida where he improved very much, gaining weight and noting marked diminution in his cough and expectoration. While he was there, lipiodol instillation was done and the patient presented this bronchogram at the time of his first visit. He now complained of cough, profuse expectoration and occasional night sweats. Physical examination revealed a rather emaciated, slight man, markedly plethoric. Essential physical findings were as follows; dullness over the entire left lung from apex to base; diminished bronchovesicular breathing over the whole left lung, with many medium and coarse moist

râles. No clubbing of fingers was noted. Fluoroscopic examination showed an exudative productive lesion involving the greater part of the lung structure on the left with many annular shadows occupying the upper half of the left lung; the trachea, heart and mediastinum were displaced to the left. The interspaces on this side are narrowed and the diaphragm elevated. On fluoroscopy there was a definite shift of the mediastinum to the left on inspiration and a return to former position on expiration. On a regimen of postural drainage and a high caloric diet and small doses of sulfonamides the patient improved, so that on March 10, 1945, the exudative process had entirely diminished and the areas of fibrosis and cystic bronchiectasis became apparent. We believe that this is an instance of cystic bronchiectasis complicated by repeated infection, making it very difficult to distinguish from the acquired form. The sharply defined annular shadows seen on the last roentgenogram without surrounding parenchymal infiltration, tend to confirm this opinion.

#### CASES COMPLICATED BY SPONTANEOUS PNEUMOTHORAX

*Case 8.* N. G., a 31 year old white male, was first seen at his home complaining of sudden severe pain in his left chest; this was accompanied by marked pallor. The onset was about three days prior to this examination and, as stated above, was ushered in by severe left chest pain. The patient went to the Newark City Hospital, where his chest was strapped and then he was allowed to go home. Symptoms improved the following day; however, 24 hours after the initial episode, the pain recurred and the patient became extremely pale. Physical signs revealed a right hydropneumothorax with hyper-resonance and diminished breath sounds above the fifth posterior rib, dullness and absent breath sounds from there to base. He was admitted to the Newark Beth Israel Hospital where roentgenographic examination showed a right hydropneumothorax with displacement of the heart and mediastinum to the right. Chest paracentesis revealed a frankly bloody fluid which did not coagulate on standing. The chest cavity was emptied of this material and rapid reëxpansion performed by means of oxygen lavage. The true nature of the disease was now revealed, since roentgenographic examination showed several bullae at the apex of the left upper lobe with a similar lesion in the contralateral lobe.

*Case 9.* C. H., a 43 year old white male, was admitted to the Newark Beth Israel Hospital because of dyspnea and weakness. The patient had had symptoms of diminished cardiac reserve for one year prior to admission. For the last six months he had had attacks of nocturnal paroxysmal dyspnea and coughing. Physical examination revealed a poorly nourished man, orthopneic and dyspneic; neck veins were distended. There was cyanosis of the lips and fingernail beds with clubbing of fingers and toes. The heart showed its point of maximum intensity in the fifth space outside the midclavicular line; heart sounds were of fair tonal quality. A high pitched systolic murmur was heard at the mitral area. Pulse rate and ventricular rate were 120 per minute; blood pressure was 180 mm. Hg systolic and 130 mm. diastolic. Fine moist râles were noted at the lung bases. The liver was palpable four fingers below the costal margin. The patient was placed on bed rest, digitalized and given appropriate therapy for congestive heart failure; however, the dyspnea was unrelieved. Roentgenographic examination revealed the true cause of his respiratory difficulty; a large spontaneous pneumothorax presented itself. In the underlying lung parenchyma, several well defined annular shadows could be seen, clearly demonstrating the cystic nature of the parenchymal disease. After oxygen lavage the lung reëxpanded and the signs of failure promptly improved. The patient became subjectively well and was discharged from the hospital under digitalis medication. It is interesting to note that for the past three years he has been working as a barker in a circus.



FIG. 10.

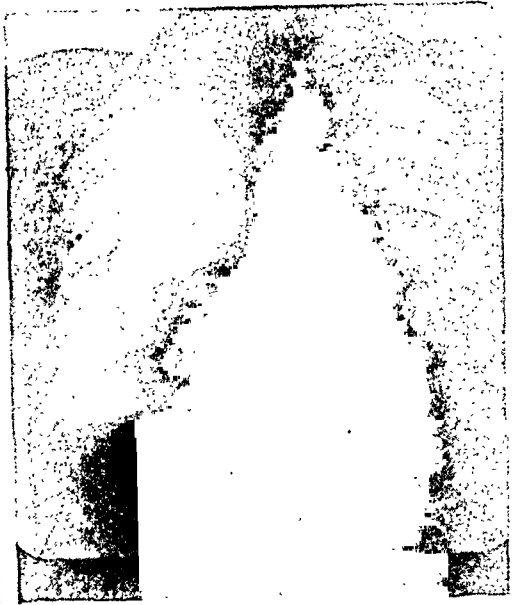


FIG. 11.



FIG. 12.

FIGS. 10, 11, and 12. *Case 9.* Cystic disease complicated by spontaneous pneumothorax. Figure 10 shows spontaneous pneumothorax in patient with hypertensive heart disease and congestive failure. Several thin-walled annular shadows may be seen in partially collapsed right upper and middle lobes. Figures 11 and 12 show reexpanding right lung; the annular cystic spaces are better seen on original roentgenogram than in reproduction.

## ACQUIRED CYSTIC DISEASE

*Case 10.* Ayerza's disease with acquired pneumatocele. C. G., a 41 year old Spaniard, was admitted to the medical service of the Newark Beth Israel Hospital in March, 1940, complaining of exertional dyspnea, orthopnea, marked cyanosis and swelling of both ankles of two years' duration. The past history is significant in that he had always been well until 1911, when he developed bronchial asthma with frequent episodes of respiratory difficulty. At the age of 22 the patient had a penile sore for which he received 12 intramuscular and 12 intravenous injections. However, despite this apparently inadequate therapy, his serologic reaction remained negative since 1925. His present illness began insidiously with increasing dyspnea, blue-black cyanosis, and marked orthopnea. Physical examination revealed the following pertinent findings: Scleral vessels were dilated and of a definite bluish hue. Pupils were equal and reacted to light and accommodation; fundi showed a marked degree of cyanosis and the retinal vessels were dilated. Cervical veins were distended but did not fill from below. Skin and mucous membranes were of an extreme purple color, evidence of the severe cyanosis. The chest was barrel-shaped and kyphotic. The percussion note was hyper-resonant throughout with diminished breath sounds and prolonged expiratory phase and many sibilant and sonorous râles. The heart was definitely enlarged; the point of maximum intensity was in the sixth space outside the midclavicular line. The sounds were of poor tonal quality; there were no murmurs;  $P_2$  was greater than  $A_2$ ; sinus rhythm was regular. The pulse and ventricular rates were 86 per minute and blood pressure readings were established at 164 mm. Hg systolic and 90 mm. diastolic. The liver was down three fingers'-breadth below the costal margin and the spleen one finger's-breadth. The extremities showed bilateral clubbing of the fingers and toes, marked cyanosis of the nail beds, and pitting peripheral edema.

Laboratory data: Hemoglobin 130 per cent, red blood cells 6,250,000, white blood cells 6,000 with a normal differential count. Venous pressure—13 cm. of blood. Blood and spinal fluid serologic reactions negative.

Electrocardiogram showed a right axis deviation; peaked P-waves in Leads II and III.

Roentgenographic examination of the chest showed evidence of bilateral emphysema with a large pneumatocele in the left lower lung field. The latter probably arose as a result of prolonged bronchial asthma, chronic bronchitis and peribronchitis, increased intra-alveolar pressure due to the failure of egress of air during expiration, rupture of alveolar septa and cystic formation. We believe that this case illustrates the usual sequence of events in the acquired form of cystic disease.

Under a régime of therapy for the congestive failure and frequent phlebotomies, the patient got along fairly well.

*Case 11.* N. B., a 35 year old white baker, was first seen at the chest clinic of the Newark Beth Israel Hospital on December 17, 1940. The patient was perfectly well until 15 years prior to this, when he noted an insidious onset of cough and expectoration of a thick white tenacious sputum, never foul smelling. He had no hemoptysis, night sweats, anorexia or weakness. The patient was referred to the Newark Board of Health, because of an abnormal shadow seen in his chest on routine fluoroscopy prior to obtaining a food handler's certificate. His past history is significant only in that he had frequent "colds" and asthmatic seizures during the past 15 years, with frequent attacks of allergic rhinitis and urticaria. Physical examination was negative except for the chest which showed generalized hyper-resonance and diminished breath sounds. An occasional rhonchus was heard in the right chest. Roentgenographic examination showed evidence of bilateral hyperillumination of the lung fields. A large thin-walled annular shadow could be seen in the medial portion of the right lung field. On bronchography, no contrast substance was found

to enter the cystic space. However, the bronchi in the surrounding lung tissue were visualized and bunched in the contiguous lung parenchyma. Diagnosis: Chronic bronchitis and emphysema with large pneumocyst in the right lower lobe.

*Case 12.* E. J., a 48 year old coal miner, was first seen by one of us complaining of frequent "colds" and asthma. The patient had a definite exposure to silica dust, having been a miner in Scranton, Pennsylvania, from 1920 to 1932. He had had a chronic hacking cough for 12 years, only occasionally productive of small amounts of phlegm. Recently, his cough had become worse and he noted dyspnea on exertion.



FIG. 13.

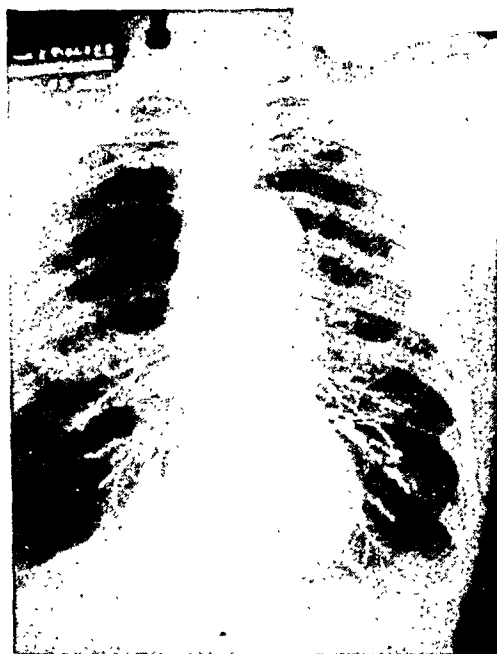


FIG. 14.

FIGS. 13 and 14. *Case 12.* Acquired cystic disease. Acquired pneumatocele in a silicotic coal miner. Figure 13 shows large pneumatoceles of right upper lobe, right lower lobe and left lower lobe; note absence of lung markings. An occasional trabecula could be seen coursing through the cystic area of the right lower lobe. In figure 14 bronchogram fails to show the contrast medium in any of the cystic areas. Cylindrical bronchiectasis may be seen bilaterally.

Physical examination was negative except for the following: There was slight clubbing of the fingers. The chest was definitely barrel-shaped with increase in the anteroposterior diameter. There was marked hyper-resonance to percussion bilaterally. Sibilant râles and wheezes could be heard over both lung fields with a few medium moist râles at the bases. The heart disclosed nothing of importance. Fluoroscopic examination confirmed by roentgenographic studies showed markedly brilliant illumination over the upper one-third of the right lung field. No lung markings could be visualized in this area; over the lower one-third of this same lung field another area of hyperillumination could be seen. On closer scrutiny, small strands traversing this cystic space were revealed. Intervening between both of these areas, a region of normal lung tissue with increased bronchovesicular markings was discernible. A similar area of hyperillumination could be seen at the left lower lung field. On bronchographic examination, no contrast substance entered either cystic space although the contiguous bronchi appeared dilated. Diagnosis: Obstructive pulmonary emphysema; emphysematous bullae; chronic bronchitis and peribronchitis; probable silicosis, although roentgen appearance not entirely diagnostic.

## SUMMARY

Cystic disease of the lung may exist in the congenital and acquired forms. The pathology, pathogenesis, clinical and roentgenologic characteristics of each form are discussed. Cases illustrating steps in the pathogenesis of the congenital form (cases 1, 4), and its various complications—hemorrhage (cases 2, 3, 4, 5), infection (cases 6, 7), spontaneous hemopneumothorax (case 8), and spontaneous pneumothorax (case 9) are presented. The acquired form of the disease and its association with chronic bronchitis, peri-bronchitis, pulmonary fibrosis and bronchial asthma are illustrated in cases 10, 11, and 12.

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# A BRIEF REVIEW OF ARTHRITIS AND ALLIED CONDITIONS IN TROPICAL DISEASES \*

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MEN are being returned to the United States in increasing numbers from regions where they have been exposed to tropical diseases, hitherto largely unfamiliar to most physicians in this quarter of the world. Many of these diseases have already made their appearance in this country. Some, though not primarily classed as arthritides, present joint phenomena as part of their symptomatology. Many others have painful manifestations in various parts of the body, including the limbs. A description of such phenomena as they occur in tropical diseases may be of aid in diagnosis and in their differentiation from the better known diseases of joints as seen in temperate climates.

Arthritis is well known as a complication of a few tropical diseases and may occur, though less commonly, in many others. In the former group are bacillary dysentery, fungus infections such as coccidioidomycosis and Madura foot, filariasis and undulant fever. Somewhat less frequently one finds arthritis in patients with yaws, bejel, relapsing fever, rat bite fever, sporotrichosis, histoplasmosis, leprosy, smallpox, scurvy, tropical ulcer, dracontiasis and onchocerciasis. A few diseases practically never have associated arthritis. These include amebiasis and the leishmania infections.

Apart from definite arthritis, aches and pains in the joints are common in a wide variety of tropical diseases. In addition, in certain groups of diseases, notably the rickettsial, the viral and the spirochetal diseases, pains in the limbs, together with headache, backache or generalized body pains are so severe and so regularly present as to be of frequent assistance in diagnosis.

We exclude from the present discussion such diseases as tuberculosis, typhoid fever and the venereal diseases as well as the vitamin deficiencies, since they are prevalent in temperate climates as well as in the tropics.

Among the viral diseases, *dengue* is outstanding as a cause of pain. As part of a picture that includes severe generalized aches and pains, dengue may give pain in all of the larger joints, most intense in the knees, hips and back. Actually, it is the tendinous insertions about the joints which are the painful points rather than the joints themselves, and passive motion is painless. The pains appear with the rise of fever, often decrease as the fever diminishes and recur when the temperature again rises. Such pains appear in over 50 per cent of the patients and are often intense enough to merit the name "break-bone." There is usually no inflammation in the affected joints, though a few patients may show periartthritis of the knees or ankles which

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may persist for months. Walking may be difficult and stilted and pains in the hands and soles may continue for many weeks. In the end complete recovery is the rule.

The symptoms of *sand-fly fever* are similar to those of dengue.

*Yellow fever* does not usually present evidence of joint involvement. However, severe pains in the limbs, neck and back along with intense headache are often characteristic at the onset and may increase in succeeding days.

Serous or purulent arthritis has been described as an occasional complication of *smallpox*. In a few cases, ankylosis has occurred with resulting deformity. Generalized pains, including headache and pronounced backache, are characteristic.

Generalized pains are present in both *psittacosis* and *Rift Valley fever* and, in the latter, affect the back, shoulders and legs particularly.

Among the fungus infections *coccidioidomycosis* is a disease of special importance in the United States. Rosenberg<sup>3</sup> and his associates have summarized our recent knowledge of coccidioidal arthritis. The main reservoir of this infection in the United States lies in the Sacramento-San Joaquin Valley in Southern California. About 90 per cent of the cases reported in this country have been observed in California. The disease is caused by the fungus *Coccidioides immitis*.

Involvement of joints may occur in either the acute benign phase of the disease or in the more dangerous chronic granulomatous stage and in either phase any joint of the body may be affected. In the benign stage the disease is also known as "Valley fever," "desert fever," or "desert rheumatism." This syndrome is usually mild and is often characterized by an acute onset with malaise, general aches and pains, fever, sore throat, toxic erythema and occasionally conjunctivitis and bronchopneumonia. Signs of acute arthritis occur in about one-third of all patients with Valley fever, usually appearing simultaneously with the development of lesions resembling erythema nodosum. The affected joints are tender and painful on motion and are sometimes swollen. There is no effusion or suppuration, and residual damage or deformity does not occur. In fact, although there may be considerable pain, arthritis in Valley fever is relatively insignificant and in most instances subsides completely.

Involvement of joints in the granulomatous phase of the disease is a serious affair, usually the result of a disseminated infection which may lead to death. In not more than one out of 100 patients does Valley fever develop into this more serious chronic granulomatous form, the mortality of which may be as high as 50 per cent. Bone and joint lesions are fairly common. The roentgen findings may mimic those of tuberculous arthritis, with early destruction in the region of the articular surfaces and swelling of the overlying soft tissues. The joint space may be narrowed and the articular cartilage destroyed. In the later stages the joint space may completely disappear and ankylosis result. The arthritis in these cases is predominantly destructive with little tendency to heal by production of bone.

Destruction is usually more rapid than in tuberculosis. The joint involvement is commonly an extension from adjacent bony lesions. No specific treatment has been shown to be of value.

*Histoplasmosis* is caused by a fungus, the *Histoplasma capsulatum* of Darling. It is a generalized disease with variable clinical characteristics, including fever, enlargement of the liver and spleen, anemia, leukopenia, adenopathy and pulmonary symptoms. The initial manifestation is sometimes a small skin lesion which may develop into a generalized ulceration.

Key and Large<sup>2</sup> have reported histoplasmosis involving the knee joint clinically resembling tuberculosis. In their patient, a dull ache and disability progressed for over seven months. There was no history of trauma. The knee was enlarged and there was thickening of periarticular tissues. There was moderate increase of local heat, without redness of the joint. Roentgenographic examination showed thickening of soft tissues and moderate atrophy of bone. Aspiration yielded thick purulent material negative on culture. At operation the synovial cavity resembled a large abscess filled with thick gray pus, grossly resembling advanced tuberculosis, while microscopically the synovial membrane was found to be transformed into a mass of granulation tissue infiltrated with giant cells and macrophages. Many of the phagocytic cells contained the *Histoplasma*, some of them in enormous numbers.

Another fungus disease with articular involvement is *Madura foot*. Although this chronic inflammatory disease usually attacks the foot, it may involve the knee, thigh, buttock and rarely, the hand. Characteristically, there is marked swelling or deformity of the part with progressive disintegration of all the tissues, including the bones and joints, and granulomatous nodules on the surface with sinus openings.

Other fungus diseases such as *sporotrichosis* and *actinomycosis* may attack muscles, bones or joints with their chronic inflammatory lesions.

Among the helminth infections, *filariasis* in the stage of invasion is not infrequently accompanied by synovitis. An arthritis or a synovitis may develop in the knee or hip, occasionally with purulent effusion. In some instances fibrous ankylosis has been reported following filarial infection.

Transient swellings about joints have been noticed at times as the first symptoms of *loiasis*. In some cases, these swellings are painless; in others there is aching or burning together with swelling in a hand, arm, wrist or ankle.

Acute arthritis has been described in *onchocerciasis* with micro-filaria in the joint fluid in some patients. It is more common, however, to find small or large subcutaneous tumors in proximity to joints, especially around the knee and in the popliteal space or over the trochanters, about the elbow or about the vertebral column. The swellings may be as large as a pigeon's egg and may be painful in the incipient stage. In some cases pain is present and fistulae form, with the nodule acting as a purulent focus. Loss of function may result. Scarring frequently occurs, especially about the trochanters.

In countries in which *guinea worm* infection is endemic, this diagnosis is always suggested when a bullous blister or a sinus appears on the foot or leg. Such sinuses may be single or multiple. If the worm is near a joint, that region may become red, swollen and painful and walking may be difficult. Arthritis and synovitis frequently develop with a serous or purulent joint effusion, usually sterile. There may be fibrotic changes and contraction of a tendon such as the tendo Achilles or the hamstrings, or bony ankylosis may occur. Permanent deformity may result from secondary bacterial infection, particularly when rest in bed has been prolonged. The joint changes are induced by invasion of the joint by the guinea worm itself or merely by the nearby presence of a calcified worm. In some cases, the live worm burrows deep between fascial planes producing pains in the vicinity of joints without actual joint involvement.

Other helminth infections which may be accompanied by generalized body pain include *schistosomiasis*, *cysticercosis* and *trichiniasis*. In the latter disease mild or severe muscular pains occur particularly at the beginning of the period of larval migration into the muscles.

Protozoal diseases which may be associated with generalized aches and pains and discomfort in the vicinity of joints include malaria and trypanosomiasis. Severe headache and pains in the back and about the joints are commonly experienced during the high fever which accompanies a malarial attack. Muscular soreness may also be a symptom. Even during the premonitory stage of the disease and in chronic more or less afebrile cases, rheumatic pains frequently occur. Blackwater fever is often accompanied by severe lumbar pain.

Neuralgic pains, especially near the joints, are frequently seen in the early stages of *trypanosomiasis* (African sleeping sickness). Some patients may develop painful swelling of the feet and hands or of joints elsewhere. This may disappear after a few days to reappear at another site. Deep hyperesthesia with severe pain following slight trauma may be present especially over bony prominences (the so-called Kerandel's sign). Pains and cramps may be present in the late stages also.

Among the spirochetel diseases, those which have joint manifestations as part of their symptomatology include bejel, yaws, relapsing fever, infectious jaundice (or Weil's disease) and rat bite fever. In *bejel*, the non-venereal treponematosis of the Euphrates Valley, the causative organism is indistinguishable from *Treponema pallidum*. This disease often shows bone changes: periosteal or endosteal proliferation with or without areas of rarefaction, or in some cases lesions resembling gummata and involving the medulla. These last may extend to the end of the bone and into the joint, producing localized destruction of the articular cartilage of one surface of the joint. Proliferative changes may develop about the areas of bony destruction.

The treponema (*T. pertenu*) responsible for yaws is another organism indistinguishable from the causative agent of syphilis. Joint pain may occur

at any stage of the disease in yaws. During the incubation period rheumatic-like pains, worse at night, may be noticed in the joints or in long bones. In the secondary stage, pains in bones, joints and muscles not infrequently accompany the irregular fever and headache. In the late stage of yaws, bones and joints may be affected in a fashion similar to that of syphilis. In some cases, one may find hydrarthrosis, in others a chronic infiltration of the synovial or perisynovial tissues, tenosynovitis or chondrosynovitis. Occasionally an entire joint may become disorganized. Ankylosis may occur and may render useless a finger, hand, large joint or whole extremity. Another feature of yaws, typical though rather infrequently seen, is the bow contraction of the little finger or less commonly of the fourth finger found in the late stage of the disease. The primary change, viz., contraction of the skin, is followed by shrinkage of the joint capsule and the deformity described.

Subcutaneous nodules are often present in yaws, most commonly on the ankle or leg. They may soften and lead to lesions of bone and deformities with deep ulceration and scarring, particularly where the bone is close to the skin. Joints may be affected secondarily from these nodules. One may also find juxta-articular nodes symmetrically placed in relation to joints, e.g., over the olecranon or over the lower ends of the femora. These nodes are movable at first, later becoming fixed.

Bone and joint sequelae may occur in as many as 20 per cent of patients with yaws with severe pain often an outstanding feature.

In *relapsing fever*, severe pains may constitute the most prominent symptom at the onset, persist throughout the course of the fever and recur when the fever recurs. They closely resemble the pains of dengue and may be present in the back, neck and loin and in the muscles, bones or joints of the limbs. In most instances, there is no real inflammation of the joint, though arthritis has been noted in some epidemics and polyarthritis has been reported as a complication in convalescence.

Muscle and joint pain is frequently present in *Weil's disease* (leptospirosis or infectious jaundice). Agonizing pain in the back and limbs, particularly in the calves, perhaps with great tenderness, often marks the sudden onset of the disease and should suggest the diagnosis.

*Rat-bite fever* in the form due to *Spirillum minus* is called sodoku by the Japanese. It may give severe joint pains but true arthritis is uncommon. Bloch and Baldock<sup>1</sup> have reported a patient with pain in both knees and in the left ankle during the course of the disease. The case was diagnosed by finding *Spirillum minus* by mouse inoculation. Though uncommon in the naturally occurring disease, arthritis of the elbows and ankles has been frequently noted in artificially induced rat-bite fever.

Infections due to *Haverhillia multiformis*, the other variety of rat-bite fever, characteristically have a septicemia with metastatic arthritis along with morbilliform and petechial cutaneous eruptions.

Pains in the muscles occur also in certain other spirochetal diseases in the tropics, notably *seven day fever* and the *pseudo-dengue of Java*. In the latter pains in the legs are particularly prominent.

Among the rickettsial diseases, typhus, Rocky Mountain spotted fever, tsutsugamushi and Q fever have pains as part of their symptomatology. *Typhus fever* at its onset frequently gives pain in the limbs, especially in the calves, along with severe pain in the back and headache. These pains may be excruciating and may continue throughout the course of the disease. Such pains have on occasion led to an erroneous diagnosis of rheumatic fever. There is usually, however, no swelling or redness of the joints in typhus fever though an occasional joint effusion is encountered. Pains in the feet and legs are very common during convalescence from this disease. Similar symptoms are usually present in *Rocky Mountain spotted fever* and in *tsutsugamushi*. Pains in the back of the legs may also occur in *Q fever*.

In *trench fever* severe pains in the shin bones, particularly at night, are the classical manifestations. In some cases, even the weight of the bed clothes cannot be tolerated because of marked hyperesthesia. Joint pains are common particularly in the ankles and knees; in the chronic stages pain in the lumbar region is likely to be persistent. A distinguishing feature of all of these pains is the fact that they are uninfluenced by active or passive motion.

Joint pains are common in the chronic mild type of *Oroya fever* while a sudden onset with severe joint pain particularly in the knees, ankles and wrists, often marks the onset of the *Verruga peruviana* stage of the disease.

Among the tropical diseases caused by bacteria, joint manifestations are common in several, especially in bacillary dysentery and leprosy. Tularemia and undulant fever may also show joint involvement but need not be discussed as tropical diseases. Plague and cholera exhibit painful phenomena in the course of disease. In *bacillary dysentery* arthritis occurs in a variable percentage of patients, from 0 to 16 per cent in different epidemics. It is more common in Shiga infections than in others. The joint involvement occurs most frequently from one to three weeks after the onset of the dysentery but has been known to appear months later, occasionally after all symptoms of a previous mild dysentery have been forgotten. Single or multiple joints may be affected. One or both knees may be involved. Next to the knees, the ankles are most susceptible to attack. Dysenteric arthritis may persist four to six weeks but in the end complete recovery and return of function are to be expected. Suppuration with resultant ankylosis has occasionally been encountered, but is rare. The joint effusion in bacillary dysentery is usually straw colored and is slightly viscid. As a rule the joint fluid is sterile, though occasionally *Shigella* organisms are cultivated, and agglutinins are sometimes present in higher titer in the joint fluid than in the blood itself.

In contrast to its frequent occurrence in bacillary dysentery, arthritis is seldom, if ever, found in patients with amebic dysentery.

Severe generalized pain in the limbs and back commonly accompanies the onset of *leprosy*. Soon after, painful swelling of the hands and feet may appear. Later, contractures are common, as in the hand, with the resulting *main-en-griffe*. Excruciating pain in the toes, especially the big toes, may be present. Trophic disorders of bones and joints may develop with or without ulcerations and rarefaction and absorption may take place with gradual disappearance of bones and joints, especially in the phalanges of the hands and feet. With certain joints, especially the wrists and ankles, one occasionally sees an actual neuropathic process akin to a Charcot joint, with disorganization of cartilage and bone.

In *cholera* muscular pains in the limbs due to loss of fluid and electrolytes come on acutely and disappear rapidly with replacement therapy.

Pains in the back and limbs may occur in the prodromal stage of *bubonic plague*. If the plague bubo forms in the groin, as is usual, the leg may be held in flexion to avoid pain. With the bubo in the axilla, the arm is likely to be held in abduction. Careful examination differentiates this from actual joint pain.

Other tropical diseases of uncertain etiology may attack joints or produce pain simulating arthritis. In *ainhum*, a circular groove appears at the base of one or both little toes, less often the fourth toes. This groove gradually deepens and within a few years, as a rule, proceeds to the severance of the toe, usually without pain or ulceration. The bone beneath the constricting band has become rarefied and then absorbed.

*Tropical ulcer* is likely to occur on the lower portion of the foot or leg. When on the dorsum of a toe, the ulcer sometimes burrows downward to involve tendons or a joint cavity.

Pains in the back together with weakness of the legs are frequent signs at the onset of *lathyrism*, a disease not infrequent in India, Africa and other tropical countries. Spastic paralysis with ataxia are the prominent symptoms of this disease, whose etiology is thought to be the consumption in large amounts of products made of the chick-pea or a contaminating weed.

The etiology of *pyomyositis* is unknown. The disease is found particularly on the African gold coast and usually attacks the gluteal or quadriceps muscles. It may be mistaken for septic arthritis or cellulitis.

On occasions, various drugs used to treat tropical diseases may be the cause of pain in muscles or joints. Muscle cramps may occur in *aspidium* poisoning. Generalized body pains have followed the use of certain drugs employed in treating African trypanosomiasis, namely *antrypol* (the English equivalent of Bayer 205) and *tryparsamide*. Muscle stiffness may follow the intravenous injection of *antimony* preparations used for treatment of oriental sore or kala azar. Toward the end of the course of therapy, an injection may be followed after several hours by severe pains in muscles and joints along with cramps in the calves.

In addition to the joint manifestations of tropical disease, one may find all the more usual forms of joint disease in the tropics. Their prevalence

in temperate and in tropical regions differs somewhat, however. In the tropics, both rheumatoid arthritis and rheumatic fever are relatively uncommon, though they may occur with their usual frequency among European residents in many tropical areas. Some experienced workers in Central Africa, South China, India and Malaya report never having seen rheumatic fever or endocarditis in a lifelong experience in those countries. By contrast, one finds tuberculosis of the joints to be extremely common in the tropics probably because these regions have been largely unsanitated and the incidence of tuberculous infection in general is very high there. Gonorrheal arthritis has also been reported commonly in China, India and Ceylon.

#### SUMMARY AND CONCLUSIONS

From the standpoint of involvement of joints, tropical diseases fall into three groups: (1) diseases in which arthritis is a well-known and comparatively common complication; (2) diseases in which arthritis occurs occasionally or incidentally, perhaps as an extension from more characteristic lesions elsewhere; (3) diseases in which arthralgias and myalgias occur without definite joint involvement. (In many of these arthritis is simulated.)

Knowledge of the occurrence and course of arthritis in association with tropical diseases should contribute to accurate diagnosis of the disease and to proper assessment of prognosis for the complication.

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## LIPOID PNEUMONIA IN ADULTS \*

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THAT the problem of lipoid pneumonia is not one primarily of infants and children is indicated by the marked increase in the number of cases reported in adults in the past five years,<sup>1</sup> which now equal in number those observed in infants.<sup>2,3</sup> In 264 cases compiled from 1927 through 1942, Sweeney<sup>3</sup> found 133 in infants and children and 131 in adults. Hence, the condition is not as uncommon in adults as previously thought. Of these, only 44 could be definitely ascribed to the use of intranasal mineral oil. The use of mineral oil as a laxative accounted for nearly half of the adult cases, whereas vitamin oils were the outstanding causes in children and infants, accounting for over one-third of the cases.

As Ikeda<sup>4</sup> has pointed out, the term *lipoid pneumonia* should be strictly confined to a productive inflammation of the lung in which the fundamental histologic alterations are directly attributable to the presence of foreign oil or fat. A few oil-laden macrophages and oil globules due to agonal or terminal aspiration in acute exudative or septic pneumonia, he pointed out, are not the criteria of this condition. The etiologic factors in adults and older children are often such that the cases may well be considered in a separate group. Ikeda has applied the term *paraffinoma* to these pulmonary infiltrations, which often simulate carcinoma of the lung in radiologic appearance. Houck<sup>5</sup> has followed a similar trend, and Saenz<sup>6</sup> also has considered the classification into adult and infantile types as important. Hence, a classification into adult and infantile types has been well established. The great variations in the clinical picture of this disease in adults and the greater variety of diseases seen in the chest as age advances make it a difficult diagnostic problem in the adult group.

Our concern in this report is exclusively with those clinical pictures occurring in adults. Since some of the types termed infantile occur in adults, our discussion concerns symptom complexes regarded as infantile<sup>4</sup> as well as those considered essentially adult in type. Both so-called infantile and adult types may occur in either adults or infants,<sup>7</sup> and the pathogenesis is fundamentally the same.

Clinically, the expressions of lipoid pneumonia may be grouped as follows:

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I. *Asymptomatic*

- A. Not recognized before autopsy.
- B. Physical findings leading at times to a roentgenologic diagnosis.
- C. Findings on roentgenologic examination without remarkable physical findings.

II. *Symptomatic*, with the findings in B and C, above, expressed as

- A. Acute pneumonitis simulating aspiration pneumonia; protracted bronchopneumonia.
- B. Recurrent acute pulmonary infection with clinical evidences of repeated attacks of bronchopneumonia.
- C. Low-grade bronchial or pulmonary infection which leads to roentgenologic findings.
- D. Picture simulating carcinoma of the lung, with cough, pain in chest, and related symptoms leading to roentgenologic findings which simulate those of carcinoma.
- E. Lipoid pneumonia incidentally found in association with other pulmonary disease.
- F. Association of any of the above pictures with a clinical state predisposing to aspiration, such as bulbar palsy, multiple sclerosis, other causes of dysphagia, and severe debilitating disease.

The predominant occurrence of the asymptomatic group is well shown by reports in the literature. About one-half the autopsied series of Freiman, Engelberg and Merrit<sup>1</sup> was asymptomatic. The frequency of the asymptomatic group makes it difficult to determine the actual incidence of lipoid pneumonia. As Cannon<sup>8</sup> pointed out, most of the cases reported have been diagnosed at necropsy. The incidence probably varies widely geographically for the reported incidence of lipoid pneumonia at autopsy varies widely; for example, six in 290 consecutive autopsies,<sup>9</sup> seven in 101 consecutive autopsies,<sup>10</sup> 41 in 3,500 consecutive autopsies<sup>1</sup> in adults, and 39 in 2,000, 27 of which were adults.<sup>8</sup>

The frequency of the asymptomatic group in one autopsy series<sup>1</sup> was approximately 25 per cent. Of 41 cases, 10 showed no symptoms or signs. In four of these roentgenograms were taken which were negative. These fall in Group I-A of the classification given. Of this group of 41 cases, there were 10 with no known pulmonary symptoms but with either physical signs, roentgenologic evidence, or both. These constitute examples of Groups I-B and I-C of the clinical classification. The accidental finding of roentgenologic evidence of pulmonary infiltration, when chest plates are taken in periodic examinations or evaluations without regard to symptoms, produces these clinical groups.

The roentgenologic findings vary widely depending on, among other factors, the type of oil, the mode of aspiration, the "dose," and the extent of the process. We have already mentioned cases in which roentgenologic findings

were reported as normal, or within the range of normal variation of pulmonary shadows, when postmortem examination revealed the presence of lipoid pneumonia. In many instances exaggeration of the bronchovascular markings in the lower lobes may be the only evidence. Small areas of increased density may appear along the bronchial markings. Evidence of fibrous and atelectatic areas may develop in the surrounding parenchyma. This comes about apparently from the mononuclear cellular reaction to the oil in the alveolar spaces. These cells pass to the lymphatics causing engorgement, nodulation, and beginning fibrosis. Nodulation may appear and when lesions reach sufficient size areas interpreted as consolidation are seen. These areas are often more sharply defined than those of bronchopneumonia and are often not limited by the usual anatomic subdivisions of the lung.<sup>11</sup> The areas of nodulation are frequently very sharply defined, giving the appearance seen in bronchogenic carcinoma. This will be discussed further below. At times they may be feathery. Again they favor the bases, especially the right base, and tend to spread from the hilar areas. The upper lobes may be involved but if they are, only rarely are the lower lobes free. Hence, the picture varies from one of delicate or heavy linear markings to nodulation and consolidation. Without secondary bacterial infection in the lungs, the shadows do not change in size greatly from month to month. They may increase in size slowly. The fibrous changes may cause contractions of shadows seen in the more acute stages as time goes on. Superimposed secondary infection may cause the shadows to vary from time to time. Compensatory emphysema occurs.

It can readily be seen from these descriptions how easily confusion may occur with bronchiectasis, tuberculosis, primary and secondary malignancy, pulmonary infarction, acute bronchopneumonia, unresolved pneumonia, fungus infections and pneumoconiosis. Obviously there is no roentgenologic picture which, by itself, is diagnostic of lipoid pneumonia.

The symptomatic group contains clinical pictures simulating nearly all types of pulmonary disease. It may be felt that no classification is necessary beyond the statement that lipoid pneumonia may simulate various pulmonary diseases of other types. However, several of the pictures are outstanding and deserve emphasis. Also, stress on the similarity of lipoid pneumonia to some other pulmonary diseases is absolutely necessary to increase awareness of its possible occurrence in specific instances. Both of these facts justify the classification.

Of the six clinical types listed in the symptomatic group, that with most dramatic symptoms is Group II-A, in which acute pneumonitis, often diagnosed as acute bronchopneumonia, is found and may run a protracted course. As a matter of fact, in bronchopneumonia which does run a protracted course oil aspiration should be suspected as the cause. The type of oil may determine the symptomatology. Animal oils, especially cod liver oil, are highly irritating, whereas some vegetable oils, olive, cotton seed, sesame, and poppy seed, are relatively nontoxic. Of the common oils producing

lipoid pneumonia cod liver oil is more likely to give an acute picture of this type than is mineral oil, which is likely to produce a more chronic reaction. This has been found true experimentally in rabbits<sup>12</sup> where lipoid pneumonia resulting from cod liver oil produces a more intense acute inflammation in the early stages. Acute fatal disease of short duration has also been produced in cats.<sup>13</sup> There are a number of clinical cases of this type reported in the literature. The first two adults<sup>14, 15</sup> described as having lipoid pneumonia were similar in type to these. Both died with bronchopneumonia; both had lesions interfering with swallowing.

Without a history of aspiration or the knowledge that an oil has been instilled into the chest, there would be little reason to suspect oil as the etiologic agent in bronchopneumonia. It might be found in the sputum incidentally in a search for a bacterial cause of the disease or if looked for deliberately when the cause is suspected. Usually the lesions of lipoid pneumonia are not so extensive that the patient dies of asphyxia. In our case 1 very extensive lesions without asphyxia were noted. Superimposed infection may add sufficient strain to produce asphyxia.

Another group of pneumonias closely related to this class is the aspiration pneumonia resulting from the intake of kerosene, gasoline and other hydrocarbons<sup>16</sup> related to mineral oil.

One of the most interesting and striking of the clinical expressions of lipoid pneumonia is that considered in Group II-B. This is the picture of recurrent pulmonary infection with clinical evidences of repeated attacks of bronchopneumonia, well exemplified in our case 1.

#### CASE REPORTS

*Case 1.* J. E. B., 49-year old white male, was admitted to the hospital on August 12, 1944, complaining of shortness of breath, cough and weakness. The patient stated that his trouble began when he was 13 years old. He had had rhinitis and bronchitis at that time and had never been well since. Chronic cough had been present for the preceding 20 years. In the previous six or seven years he had had frank hemoptysis on two occasions and blood-streaked or rusty sputum numerous times since 1937. During the previous few months he had noticed progressive weakness, fatigue, dyspnea on exertion, cough and considerable expectoration of mucoid, purulent, blood-tinged, rusty or frankly bloody sputum. There was more expectoration in early morning and less trouble in dry, warm weather. He had been in numerous hospitals and clinics during the previous several years for his "lung trouble." In 1934 he was told that he had bronchiectasis. At various times tuberculosis, Boeck's sarcoid, fungus diseases and various other chronic pulmonary diseases had been considered but never proved. In November, 1941, a diagnosis of osteochondroplasia plastica was made by bronchoscopic examination. At the same time a specimen of sputum stained with Sudan III revealed the presence of fat. Questioning as to medication revealed that he had been taking "agar oil" (agar-agar and mineral oil) daily as a laxative from 1927 to 1939. He had also used an oily preparation with 2 per cent phenol (applied to the nasal mucosa with an atomizer) from 1936 to 1940.

Further historical data included mastoid operations at the ages of 18 and 19, tonsillectomy when 32, gonorrhea the same year, chancre of lip diagnosed by darkfield

examination when 36 years old. He had taken antisyphilitic therapy for 10 months but discontinued the alternating bismuth and arsenical injections because he felt weaker when under treatment.

Physical examination on admission on August 12, 1944, disclosed severe dyspnea. The patient died a few hours after admission. The temperature was 98.6° F. on admission, 102.6° F. at death. Previous examination showed a blood pressure of 110 mm. Hg systolic and 60 mm. diastolic, pulse of 88, respirations 22, temperature 99.4° F. He was a fairly well developed, poorly nourished white male, approximately 49, appearing chronically but not acutely ill. He was fairly intelligent and coöperative. Positive findings included slight injection of the pharynx, diminution of vocal resonance and breath sounds from the scapula to the lung bases bilaterally. A few basal râles were heard. There was an occasional extrasystole.

Laboratory data included a hemoglobin of 11 gm. (65 per cent), erythrocytes 3.9 million, leukocytes 7,500, polymorphonuclears 67 per cent, lymphocytes 33 per cent; sedimentation rate of 54 (uncorrected). The specific gravity of the urine was 1.021 and the urine showed an occasional leukocyte. Blood urea nitrogen was 9.1 mg. per cent; glucose, 103; serum protein 6.5 per cent; A/G 1.2/1. Kline and Kolmer reactions were negative on two occasions. Bronchoscopic examination showed multiple small osteochondromata involving the upper half of the trachea and upper portions of the right and left main stem bronchi. These were hard and the specimen removed was too small for microscopic study. Roentgenograms of the chest showed bilateral evenly distributed infiltration of midlung zones and bilateral hilar node enlargement. Sputum was negative for acid-fast bacilli four times by smear and twice by concentration.

The patient had had 11 previous admissions to the hospital, usually with bronchopneumonia superimposed on his chronic disease. These admissions were as follows:

(1) The patient was admitted February 24, 1942, discharged March 17, 1942. Low-grade fever was the only finding.

(2) The patient was admitted October 29, 1942, discharged December 7, 1942. The leukocyte count was 21,050 with polymorphonuclears 90 per cent, lymphocytes 10 per cent. The sputum was negative for pneumococcus. The temperature, 102° F. on admission, returned to normal on therapy with sulfadiazine.

(3) The patient was admitted on February 21, 1943, with a temperature of 103° F. Sulfadiazine therapy was instituted and the temperature dropped in three days. Patient was discharged on March 5, 1943.

(4) The patient was admitted on April 5, 1943. Temperature on admission was 102.6° F. and returned to normal on sulfathiazole therapy. The leukocyte count was 15,750 with polymorphonuclears 89 per cent and lymphocytes 11 per cent. The patient was discharged on April 26, 1943.

(5) The patient was admitted on July 28, 1943, with a temperature of 103° F. Sulfadiazine therapy was instituted and the temperature dropped to normal. The leukocyte count was 15,450, with polymorphonuclears 84 per cent and lymphocytes 16 per cent. Sedimentation rate was 24 (corrected). The sputum was negative for acid-fast bacilli on two examinations. The patient was discharged on August 7, 1943.

(6) The patient was admitted on October 30, 1943, and discharged on November 9, 1943. The temperature on admission was 105° F., and dropped to normal on sulfadiazine therapy. The leukocyte count was 20,000 with polymorphonuclears 89 per cent and lymphocytes 11 per cent. Sputum was negative on two occasions for acid-fast bacilli and on one occasion for fungi. Roentgenograms taken at this time were essentially the same as on all other admissions (figure 1).

(7) The patient was admitted on November 25, 1943, with a temperature of 101° F. Postural drainage was started and the temperature was down in three days. Urinalysis gave normal findings. The patient was discharged on November 30, 1943.

(8) On admission January 23, 1944, the patient's temperature was 103° F. and dropped to normal with sulfadiazine therapy. Blood culture was negative. Leukocyte count was 11,200 with polymorphonuclears 78 per cent, lymphocytes 22 per cent. The patient was discharged on January 28, 1944.

(9) The patient was admitted on February 19, 1944, discharged March 3, 1944. Temperature was 103° F. on admission and, with sulfadiazine therapy, returned to normal. Sputum examination showed oil (fat) globules.

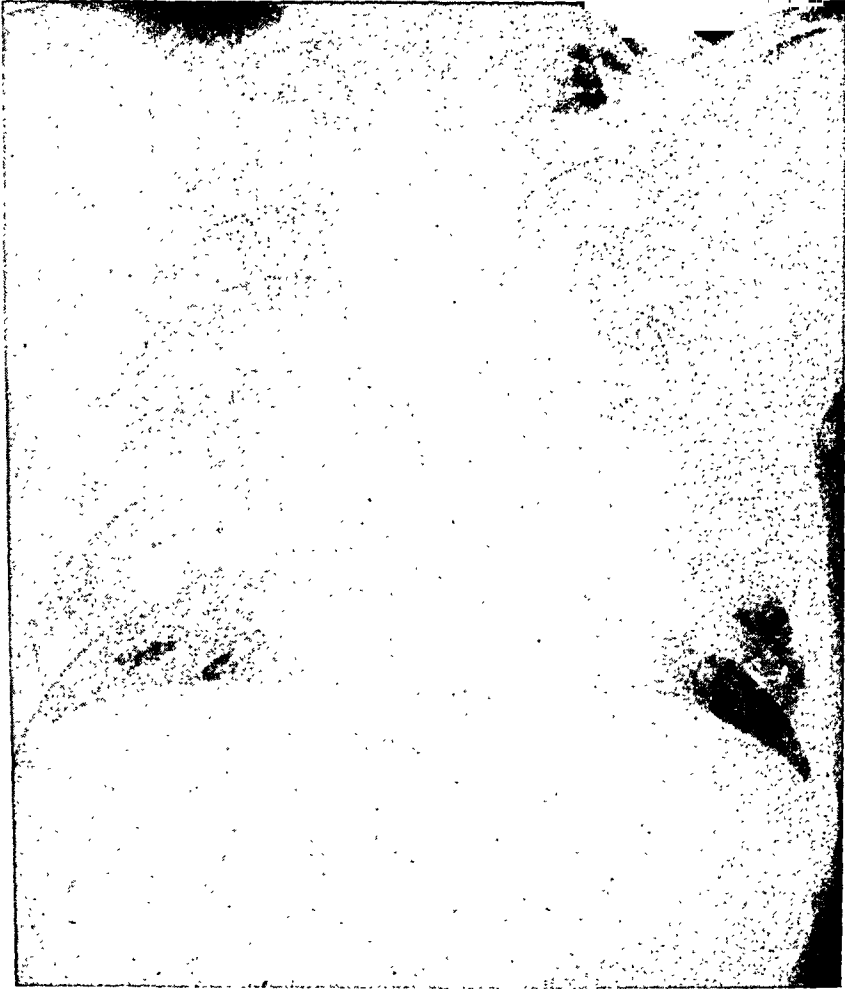


FIG. 1. Roentgenogram of the chest of Patient 1, taken on the sixth admission. It is similar to those taken at intervals from the first admission and at times when no acute infection was present.

(10) The patient was admitted on March 13, 1944, with a temperature of 102.2° F. Temperature was down in three days on sulfadiazine therapy and the patient was discharged on March 26, 1944.

(11) The patient was admitted on April 25, 1944, with a temperature of 103° F. Sulfadiazine therapy was instituted and the temperature was down in three days. Leukocyte count was 11,000 with polymorphonuclears 84 per cent, and lymphocytes 16 per cent.

Autopsy examination disclosed extensive lipid pneumonia.

A number of examples of this type of clinical picture have been published. It appears to be the one clinical type which, by itself, should arouse suspicion of lipoid pneumonia. Still the symptomatic picture is due to infection. In our patient the pulmonary changes of the lipoid pneumonia were so extensive (figure 1) that the shadows were not markedly changed during the acute episodes. Sputum studies during these episodes may not disclose any bacterial agent to produce the picture. This was true in this patient, as well as in other reported instances of this type,<sup>1, 17, 18</sup> despite the fact that high leukocyte counts and clinical pictures which are generally interpreted as resulting from bacterial types of pneumonia were obtained. In each instance, except the terminal episode, our patient responded to sulfonamide therapy with return of the temperature to normal in three to five days.

Low-grade bronchial or pulmonary infection with lipoid pneumonia may simulate closely the pictures of bronchiectasis, chronic bronchitis, pulmonary tuberculosis and other types of chronic pulmonary suppuration. Moel and Taylor<sup>19</sup> have described patients belonging to this group. Low-grade fever or transitory slight rises in temperature, chest pain, cough, productive or non-productive, together with patches of râles and areas of dullness and bronchial breathing with all gradations of these findings down to normal, make up the clinical picture. Usually such findings are basal, often confined to the right side only. Blood-streaked sputum is uncommon, but may occur. In bronchiectasis the sputum is usually more profuse, clubbing of the fingers may be seen, and the roentgenogram with lipiodol is diagnostic. So-called "unresolved pneumonia" represents a diagnosis difficult to establish and probably oil is the cause of many of these cases. Pulmonary infiltrations may not be recognized as lipoid unless the possibility is kept in mind and a possible mechanism sought when the cause of any pulmonary infiltration is considered.

In Group II-D the picture simulating carcinoma of the lung is given. We have seen one patient who has shown this picture. The following is a summary of this case.

*Case 2.* E. H., a 63 year old bottle washer in a chemical factory, was admitted to the hospital on June 25, 1943, complaining of cough and weight loss. He had felt well until one week before, but had lost an indeterminate amount of weight during the previous year. He had had "bronchitis" for the previous 20 years and had coughed up about a teaspoonful of whitish sticky sputum a day. Just previous to admission pain had developed in the right lower chest anteriorly; it was aching in character, coming on usually at night if his head was not elevated or if he lay on his right side. The pain radiated across his chest toward the sternum and had no relation to meals, exercise, or emotions. It occurred during the day if he reclined on his back or right side. He had had night sweats and chilly sensations for one week prior to admission.

The patient had had a "lump" cut off his head three years previously. Casual questioning elicited no history of medication, but close questioning indicated that he had taken an ounce of mineral oil five or six nights each week for some years to avoid constipation.

Physical examination showed a somewhat thin white male, 63 years of age, who did not appear acutely ill. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic, temperature 98.8° F., pulse 84, respirations 24. The scalp and skull showed no gross abnormalities. The thyroid gland was moderately and diffusely enlarged. There was an old perforation of the left ear drum; the eyes and nose were normal. There was almost complete edentia. The tonsils were moderately enlarged and cryptic. The chest was symmetrical. The expiratory phase of respiration seemed prolonged, and expiratory wheezing râles were heard in both lung bases posteriorly. There was increased vocal fremitus at the right lung base posteriorly. The heart appeared to be normal. The liver edge was barely palpable on deep inspiration. There was a small inguinal hernia on the right side. Rectal and genital examinations revealed no gross abnormalities. The extremities were normal; the reflexes were physiologic.

Laboratory data included a hemoglobin of 70 per cent, erythrocytes 3,850,000, leukocytes 10,150 with polymorphonuclears 74 per cent, monocytes 6 per cent, and lymphocytes 20 per cent. The urine was essentially normal except for an occasional pus cell. Phenolsulfonphthalein excretion was 55 per cent at the end of two hours. Maximum urinary specific gravity was 1.023. Blood chemical determinations showed carbon dioxide combining power 66 volumes per cent, blood urea nitrogen 15.4 mg. per cent, serum protein 6.51 gm., blood chlorides 582 mg. per cent. Kline and Kolmer reactions were negative. Mantoux test was negative. Nine sputum examinations failed to reveal tubercle bacilli. Bronchoscopic examination was negative. Electrocardiogram revealed a QRS duration of 0.14 sec., and was reported to show defective intraventricular conduction with definite electrocardiographic evidence of myocardial disease. Roentgenogram of the chest revealed an area of infiltration in the midlung zone behind the anterior end of the right fourth rib (figure 2). Bronchograms were normal.

Serial roentgenograms of the chest failed to show any clearing of the infiltrative lesion in the right lung and on July 26, 1943 (approximately one month after admission) a right pneumonectomy was done because it was felt that the patient had a bronchogenic carcinoma of the right lung. The patient had an uneventful post-operative course and was discharged two weeks later. He has been able to return to work and is being followed in the clinics.

The pathologic specimen showed the characteristic changes of lipid pneumonia with fat stains.

A number of cases of this type have been reported in the literature.<sup>4, 20, 21, 22, 23, 24, 25</sup> The first European case<sup>25</sup> showed large tumor-like shadows on which irradiation therapy was tried. The roentgen appearance of these shadows, as already described, may lead to consideration of carcinoma as a diagnosis. In our patient the findings were so typical that pneumonectomy was done and the diagnosis of lipid pneumonia made only after study of the removed lung. Brown and Biskind also reported a case in which a surgical approach was carried out apparently because of suspected malignancy. Removal of a portion of a lobe was done. It is evident, as Brown and Biskind stated, that the possibility of lipid pneumonia must always be considered when an unconfirmed diagnosis of a malignant pulmonary growth is entertained. History and sputum studies may be helpful. Differences in the course of the disease, especially by roentgen-ray studies, and bronchoscopy with biopsy material are important in the differentiation.

Group II-E includes pictures of lipoid pneumonia, any of which may take the characteristics of those described above, in association with other pulmonary disease. This group is separated from Group II-B in which bronchopneumonia occurs with lipoid pneumonia in that the repetition of that picture makes it such a unique and almost diagnostic picture that it warrants separate consideration. Also in the present group the association of the two

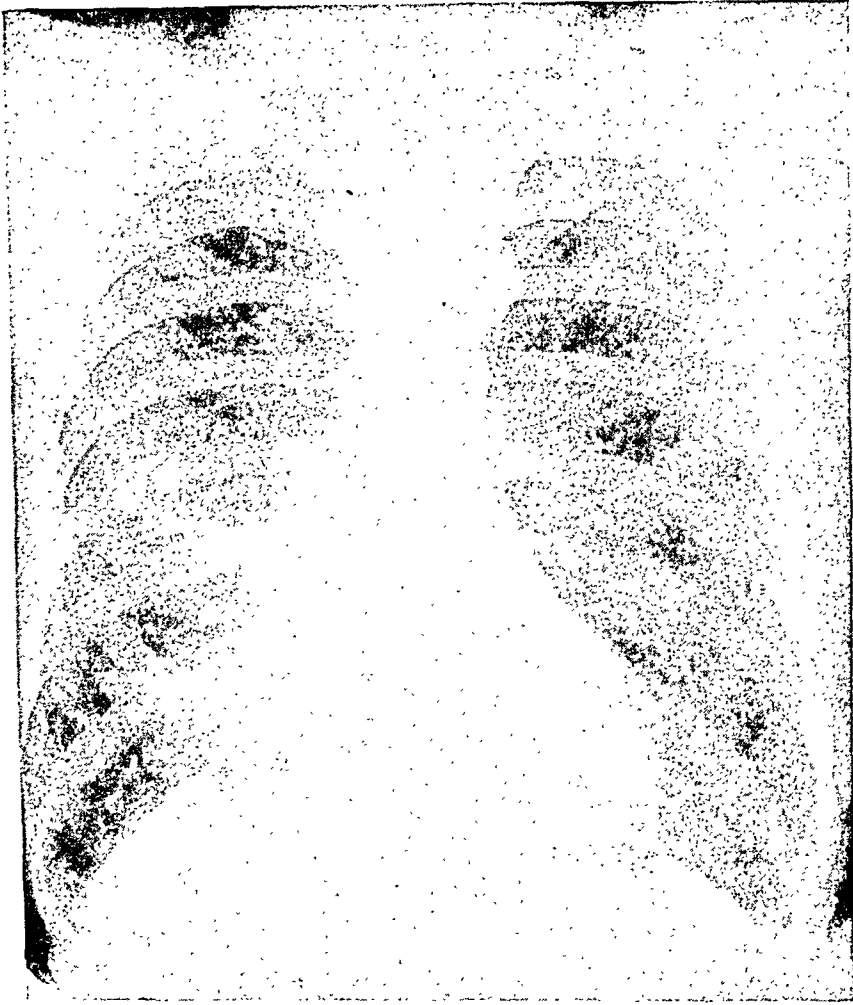


FIG. 2. Roentgenogram of the chest of Patient 2, taken on admission to the hospital, showing an area of infiltration in the midlung zone on the right side.

diseases is accidental. A good example is the case of Wood<sup>26</sup> in which lipoid pneumonia was found associated with so-called bilateral alveolar carcinoma of the lung. The question of the possible tumor-producing properties of mineral oil was discussed in that report.

The final group to be considered requires little discussion. Here the clinical pictures again may be those of any type discussed above, associated with extrapulmonary disease which predisposes to oil aspiration and which,



therefore, is likely to be found in association with lipoid pneumonia. The importance of such disease in the causation of lipoid pneumonia is widely recognized and is discussed below in the remarks on diagnosis. Bulbar palsy, cleft palate, convulsions and spasms, frequent gagging and vomiting, debilitating disease, difficulties in swallowing associated with esophageal diverticula,<sup>27</sup> cerebral birth injuries, congenital neurologic disorders, dysphagia, brain tumors, loss of cough or gag reflex, are examples. We have seen several examples of this type secondary to bulbar palsy.

Lipoid pneumonia in adults is not uncommon in the older age groups. This was not shown in our two cases, but in general the older age group predominates. The two cases do show the two chief routes of administration of the oil—the nasal and the oral. This generally results from self-administration over long periods of time. Exceptions, of course, occur at times. Whereas in infants the chief agents are cod liver and other vitamin-containing oils, milk and liquid petrolatum, in adults liquid petrolatum itself is the chief offending agent. This material cannot be metabolized by tissue enzymes whereas some of the animal and vegetable oils may be. It remains as a foreign body irritant. Inflammatory reactions with it may be due to the drug dissolved in the mineral oil.

Amounts entering the lungs depend on the dose, the frequency of application, and the effectiveness of the function of the epiglottis. Mineral oil is light and does not stimulate the cough reflex.

In adults the rôle of such predisposing factors as lesions interfering with swallowing and debilitating disease has already been discussed. Chronic infection of the upper respiratory passages may lead to the use of oily drops or sprays (sprays are more dangerous, as in our case 2), or a debilitated patient may take the oil by mouth. In infants lesions similar to those in adults, such as tracheobronchial fistula, laryngeal paralysis and esophageal disease, may contribute, but most frequently other circumstances, such as forced feeding, the administration of oily substances and attempts to feed in comatose states, are responsible. In children the pictures may be similar to some of those seen in adults, especially where mineral oil is the causative agent. Mild respiratory symptoms with a low-grade pneumonia, the repeated occurrence of superimposed infection, as described in the adult group for example, may occur. In children, too, especially if the picture is recognized early and the oil withdrawn from use, the process in the lung and the roentgenologic findings may undergo resolution.<sup>4</sup> In adults persistence of the picture and chronicity are the outstanding characteristics.

Even in cases in which a violent reaction occurs producing acute types of pneumonitis, as already stated, chronicity develops, for example in "non-resolving bronchopneumonia." The latter process represents a granulomatous productive inflammation which, when clearly localized, has a dense fibrous and neoplastic appearance.<sup>4</sup> By roentgenologic study these characteristics are brought out and malignancy may be suspected. If more widespread, tuberculosis, various types of pneumonia or bronchial disease with

secondary pneumonitis, are suspected. Periodically acute superimposed infection, recurrent pneumonia, may appear, giving a distinctive picture. Sudden or acute reactions may not appear but, after prolonged use of the oil, sometimes for years, may arise from complicating infection of various types and degrees. The condition may be found through roentgenologic study after chest findings or on routine roentgenogram without chest findings. Both may be negative and the patient go to postmortem examination with unsuspected lipoid pneumonia found at autopsy.

Although the pulmonary symptoms are said<sup>4</sup> to be essentially the same in all cases, differing only in degree or as the result of secondary infection, there are from patient to patient differences in the symptomatic picture, and in roentgenologic or physical evidences, which make for distinct clinical types. The emphasis of these types is the chief justification for our classification, for only by awareness of the possibility of the occurrence of lipoid pneumonia when such pictures arise will the diagnosis be made.

Clinical diagnosis rests primarily upon a strong suspicion of the disease when other explanations of the clinical picture are not well established. Physical findings are of little differential value, but are extremely important for they lead to roentgenologic investigation and diagnosis. Of Freiman, Engelberg and Merrit's 47 cases,<sup>1</sup> apparently only seven were diagnosed clinically. In the group collected by Bishop,<sup>28</sup> 23 of 136 were diagnosed during life. A glance at the classification of clinical pictures we have given indicates that most of the usual pulmonary diseases may be simulated or may be present as complicating disease. The history of the use of an oil, either as drops or by ingestion, increases the possibility that the picture results from oil aspiration. A defect in swallowing or a generally debilitating state adds to the picture sufficient evidence for a tentative diagnosis. It is usually stated that defects in deglutition and debilitated states are likely to occur as predisposing factors. However, many instances have occurred in healthy individuals without such states. This was true in our cases and is especially true with intranasal medication over long periods. One must remember that the history of the use of an oil is likely to be neglected and is often elicited only after the lipoid pneumonia is suspected.<sup>22</sup> Most important is the continued high suspicion of the disease in the situations already outlined. Demonstration of the lesions by roentgenograms does not settle the diagnosis, for there are no pathognomonic roentgenologic signs. Slow change in the character of lesions, with serial examinations, particularly in those located in the lower lobes, and a bronchopneumonia which fails to resolve and roentgenologic findings out of proportion to clinical symptoms and signs should lead to attempts to obtain the clinical associations described above. Confirmation may be sought by demonstration of oil in the sputum several days after oil has been discontinued as nose drops or by mouth. This may be done by letting sputum stand, then covering it with a cigarette paper to absorb the oil droplets or by microscopic search for oil. Aspiration biopsy of the lung has been advocated.<sup>18, 20</sup> In one instance<sup>20</sup> the material aspirated

by needle was allowed to settle and a layer of oil formed over the bloody material.

### CONCLUSIONS

1. The known frequency of lipid pneumonia in adults demands continued alertness for the possibility of this diagnosis when any pulmonary picture without proved cause presents itself.

2. A grouping of the clinical expressions of lipid pneumonia in adults is given. Although lipid pneumonia may simulate nearly all types of pulmonary disease a classification of the clinical expressions is necessary because several of the pictures are outstanding and deserve emphasis. Also stress on the similarity of lipid pneumonia to some other pulmonary diseases is absolutely necessary to bring this possibility to mind in specific instances.

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# THE RECOGNITION AND CLINICAL SIGNIFICANCE OF AURICULAR HEART SOUNDS \*

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THE diagnosis of cardiac disease is a clinical problem. Observation and evaluation of the sounds accompanying cardiac activity are of great importance. The electrocardiogram is of value in the analysis of arrhythmias, and is often useful in confirming a clinical diagnosis of myocardial injury. As Levine so aptly stated: "It is a general axiom that the more thoroughly one understands electrocardiography the less one needs it."<sup>1</sup> Auscultation of the heart remains a most valuable clinical procedure, not only in the recognition of valvular heart disease, but in identifying arrhythmias as well.

The problem of the systolic murmur is a generally recognized one. That a systolic murmur may be present without anatomically demonstrable cardiac abnormality is a common observation. Many are hesitant to regard a systolic murmur as significant in the absence of other findings, such as a diastolic murmur, cardiac enlargement or other evidence of cardiac disease. More recently there has been a willingness to regard as pathological systolic murmurs with certain characteristics such as accompanying thrill, harsh quality, wide transmission, long duration or loud intensity.

As a corollary to the skepticism in some quarters concerning the significance of systolic murmurs, many are prone to accept the diastolic murmur per se as evidence of cardiac disease. It is often difficult to differentiate between presystolic "murmurs" and presystolic "sounds"; and between a split first heart sound and a first heart sound preceded by an auricular sound. Misinterpretation may lead to a mistaken diagnosis of heart disease. This paper is an effort to aid in the clarification of such problems.

The physiological and pathological variations of the sounds resulting from or accompanying activity of the auricle, and an attempted explanation of the mechanism involved comprise the subject matter of this discussion.

On auscultation of the normal heart one does not commonly distinguish any separate sound accompanying auricular activity. Auricular sounds are usually faint, low-pitched, dull and of short duration, and are easily obscured by the normal first heart sound which closely follows it, since the latter is louder, higher-pitched and sharper. However, when auricular contraction occurs well in advance of ventricular systole, certain diastolic sounds may be audible.

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The stethographic records upon which this paper is based are from the Department of Medicine, Johns Hopkins Hospital.

This is best demonstrated in cases of A-V dissociation, in which, with the auricles contracting independently of the ventricles, a low-pitched sound may be heard during diastole. When recorded stethographically, these sounds occur at the peak of the a-wave of the jugular pulse, and about 0.18 second after the beginning of the P-wave of the electrocardiogram. This relationship to the electrocardiographic and pulse signs of auricular activity would indicate that these sounds are associated with such activity. In lesser degrees of heart block a sound produced by auricular activity may be noted in some patients.

That the auricular sound actually consists of two parts was stated by Sir Thomas Lewis in 1914,<sup>2</sup> and demonstrated stethographically by Cossio and Fongi in 1936.<sup>3</sup> The first part of the auricular sound was recorded during the height of auricular systole, and was recorded best by a microphone placed in the esophagus, which is in contact with the auricular wall. This sound is produced, they believe, when the blood contained in the auricles is compressed by the tense auricular walls, and results from the vibration of the auricular walls and of the compressed blood. This first part of the auricular sound is transmitted to the precordium more easily in children than in adults, in whom it is usually not heard. In children it may be heard apart from the first heart sound, especially when the auricles are contracting more actively under the influence of exercise or emotion.

The second part of the auricular sound appears *after* the height of auricular activity, and is due to the vibration of the auriculoventricular valves and to the tension of the ventricular wall. This second part results from vibrations set up by the blood ejected by the auricle, and, therefore, does not appear until auricular systole is well advanced. The second part of the auricular sound is best heard from the precordium because of its origin from the ventricles in close contact with the chest wall, and usually blends with the sounds accompanying ventricular contraction to form the normal first heart sound. It is this second part of the auricular sound which is heard in some cases of heart block, where the prolonged interval between auricular and ventricular systole prohibits such blending of auricular and ventricular elements of the first heart sound. This failure of fusion results in a sharper first heart sound as well.

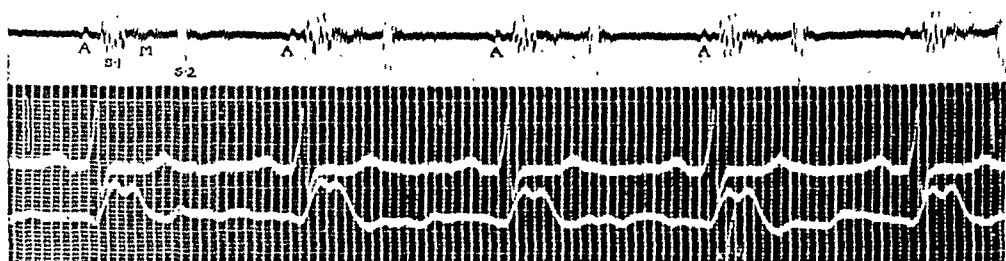
Auricular sounds may be recognized not only in patients with cardiac arrhythmia, but in patients with normal cardiac rhythm also. In children with active normal hearts the first part of the auricular sound may be audible, as mentioned above. Auricular sounds have been noted clinically and recorded stethographically in patients with hypertension (figure 1), sickle cell anemia, and Besnier-Boeck-Schaumann disease in the absence of valvular deformity or cardiac failure. A loud presystolic sound simulating that of mitral stenosis may be heard in some patients with hyperthyroidism.

A first heart sound preceded by an auricular sound must be differentiated from a split first heart sound. Usually both components of the so-called split first sound are fairly high-pitched and of almost equal intensity and

duration, and are recorded after the beginning of the QRS complex of the electrocardiogram. If the double sound at the beginning of the cardiac cycle consists of an auricular sound preceding the first sound, the auricular component is softer and lower-pitched than the ventricular component which follows it, and is recorded before the beginning of the QRS complex.

Very striking is the occasional finding of a late diastolic crescendo murmur in patients with syphilitic aortic insufficiency. Described in 1862 by Austin Flint,<sup>4</sup> this murmur, unlike the presystolic murmur of mitral stenosis, may be high-pitched and may be louder and of longer duration at the pulmonic area than at the apex. A single loud auricular sound such as occurs in patients with cardiac enlargement or failure should not be called a Flint

APEX



AURICULAR SOUNDS: HYPERTENSION

FIG. 1. The upper record is the stethogram of the heart sounds at the apex. The middle record is the electrocardiogram Lead II, and the lower record is the jugular pulse.

A: Auricular sounds  
S-1: First heart sound  
M: Systolic murmur  
S-2: Second heart sound

It will be noted that the second sound is of greater intensity than the first sound at the apex in this patient with hypertension. The auricular sound is low-pitched and is recorded before the QRS complex of the electrocardiogram.

murmur. The Flint murmur is caused by a functional mitral stenosis: blood regurgitates through a damaged aortic valve, striking the anterior mitral curtain and pushing it into the blood stream passing from auricle to ventricle, thus producing a functional mitral stenosis, inasmuch as blood expelled during auricular contraction must force a channel through the approximated valve leaflets, resulting in the production of an audible pre-systolic murmur.

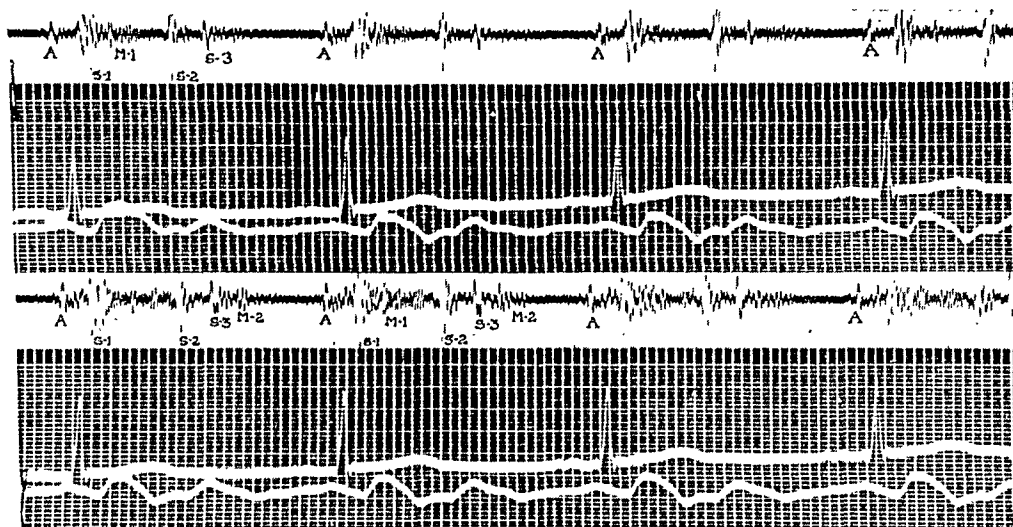
Gouley<sup>5</sup> described a characteristic deformity of the right aortic leaflet found at autopsy in 10 patients with an Austin Flint murmur: a groove directing the blood to the anterior mitral curtain.

Presystolic murmurs are most commonly encountered in rheumatic mitral stenosis, although as just demonstrated, auricular sounds and pre-systolic murmurs may be heard in the absence of such valvular involvement. There are some patients with mitral stenosis proved at autopsy in whom a systolic murmur had been the only abnormal sound noted, but who did present other evidence of cardiac disease. In mitral stenosis the first sound

may be accentuated owing to summation of the initial vibrations of the normal first sound with the terminal vibrations of the auricular sound. After a long diastole the mitral valve leaflets may be almost floated back into position before ventricular contraction, producing, therefore, a first sound of diminished intensity.

That the presystolic murmur of mitral stenosis is dependent upon effective auricular contraction is demonstrated by its absence in auricular fibrillation and its presence in patients with mitral stenosis and A-V dissociation.

APEX: SUPINE



APEX: LEFT LATERAL POSITION

#### AURICULAR SOUNDS: EFFECT OF POSITION

FIG. 2. In each of the above records the upper tracing is that of the stethogram at the apex, the middle tracing is the electrocardiogram Lead II, and the lower tracing is the jugular pulse.

- A: Auricular sound
- S-1: The first heart sound
- M-1: Systolic murmur
- S-2: The second heart sound
- S-3: The third heart sound
- M-2: The mid-diastolic murmur of mitral stenosis.

It will be noted that the record of the heart sounds with the patient in the left lateral position brings out the mid-diastolic murmur of mitral stenosis which follows the third heart sound. The auricular sound is also louder in this position, and is more easily seen to be followed by a presystolic murmur. It will also be noted that the third heart sound (S-3) is recorded at the apex of the v-wave of the venous pulse, indicating the time of opening of the mitral valve.

In the latter case a low-pitched rough murmur may be noted when the auricle contracts during ventricular diastole. In the former case the only auscultatory sign of mitral stenosis may be the mid-diastolic apical murmur produced by the rapid ventricular inflow through the stenotic valve early in diastole. During tachycardia with auricular fibrillation, however, there may be a crescendo character to the terminal part of the mitral diastolic murmur. This is caused by a summation of the mid-diastolic murmur and the normal



first sound due to the shortening of diastole, and not by auricular contraction which normally occurs late in diastole.

In mitral stenosis with normal sinus rhythm one may at times hear a mid-diastolic apical murmur and an accentuated auricular sound. Occasionally these may be present during acute rheumatic fever and disappear after the acute episode has subsided. A single auricular sound noted with the patient supine may, in the left lateral position, become louder with a pre-systolic murmur now following it (figure 2). Exercise may cause a pre-systolic murmur to be more easily heard. At times such accentuation results from the tachycardia and shortened diastole, with summation of the mid-diastolic and presystolic murmurs.

The intensity of the presystolic murmur depends upon the rate of blood flow through the mitral valve, and varies in different cycles. When the auricle contracts early in diastole with the ventricle empty the murmur is louder; it may be absent after long diastoles because of the inability of the auricle to inject blood into an already filled ventricle.

The principles demonstrated in rheumatic mitral stenosis may be applied to auricular sounds in other conditions. In an active normal heart the rapid blood flow may fill the ventricle early in diastole; contraction of the auricle completes this filling and closes the mitral valve before ventricular systole, producing an audible presystolic sound. In cardiac failure the incompletely emptied ventricle may be filled early in diastole as a result of the increased intra-auricular pressure. If this serves to approximate the valve leaflets and distend the ventricular walls early in diastole a proto-diastolic gallop may result. Systole of the dilated auricle later in diastole may produce a presystolic gallop sound.

This paper is not an exhaustive survey of the sounds resulting from auricular activity, but rather calls attention to sounds which frequently are overlooked or misinterpreted, emphasizes the importance of their clinical recognition, and presents theories concerning the mechanism of their production.

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# CASE REPORTS

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## MEDITERRANEAN TARGET-OVAL CELL SYNDROME IN AN ADULT CHINESE MALE: REPORT OF A CASE\*

By I. J. GREENBLATT, Capt., Sn.C., A.U.S., T. D. COHN, Maj., M.C., A.U.S.,  
and H. L. DEUTSCH, Capt., M.C., A.U.S.

IN an extensive report on Mediterranean target-oval cell syndrome, Dame-shek<sup>1</sup> proposed the following criteria for its recognition: (a) "The racial factor, (b) a reduction in hemoglobin concentration in association with a low color index, (c) refractoriness to iron therapy, (d) the presence of increased numbers of target cells and reticulocytes, usually in association with oval and stippled red blood corpuscles, (e) the presence of increased hypotonic resistance of the erythrocytes and (f) the absence of such conditions as hepatic disease, steatorrhea, bleeding or lead poisoning." He suggested a probable relationship between this syndrome and Cooley's anemia. It is well known that Cooley's anemia and Mediterranean target-oval cell syndrome are limited almost exclusively to those peoples who reside or whose ancestry stems from the Mediterranean area. However, an authenticated case of Cooley's anemia was reported by Foster<sup>2</sup> in a six and one half year old Chinese female whose mother had a "low grade erythroblastic anemia."

The following is the report of a case of Mediterranean target-oval cell syndrome occurring in a soldier of pure Chinese ancestry who was born in China and came to this country at the age of 15 years.

### CASE REPORT

Private L. Y., a 29 year old Chinese male, was admitted to the hospital complaining of a feeling of persistent pressure in the epigastrium for two days. He vomited three times during this period. There were no other complaints except for a feeling of weakness for as long as he could remember.

*Past History.* He discovered that he had syphilis in 1937 and had received specific therapy for the past three years. In the Army he received 30 injections of mapharsen and 12 of bismuth over a period of seven months. At no time was there a history of any reaction. On his present admission the Kahn reaction was negative.

*Physical Examination.* The patient was a fairly well nourished Chinese male who did not appear acutely ill. Examination was completely negative. Temperature, pulse and respirations were within normal limits.

The clinical impression was simple pylorospasm. He vomited once and his symptoms completely subsided at the end of 24 hours. However, the weakness persisted throughout his hospitalization.

*Laboratory Data.* A routine blood study revealed hemoglobin 83 per cent, red blood cells 6,300,000 per cu. mm., white blood cells 7,300 per cu. mm. with a normal differential. Color index 0.66. A Wright stained smear showed large numbers of polychromatophilic red blood corpuscles, a moderate macrocytosis and numerous red

\* Received for publication November 6, 1944.

blood corpuscles with basophilic stippling and a moderate degree of hypochromia. Approximately 30 per cent target cells were seen. Oval cells were present in every field (figure 1). To be certain these were target cells instead of artefacts heparinized venous blood was examined under the dark-field microscope.<sup>3</sup>

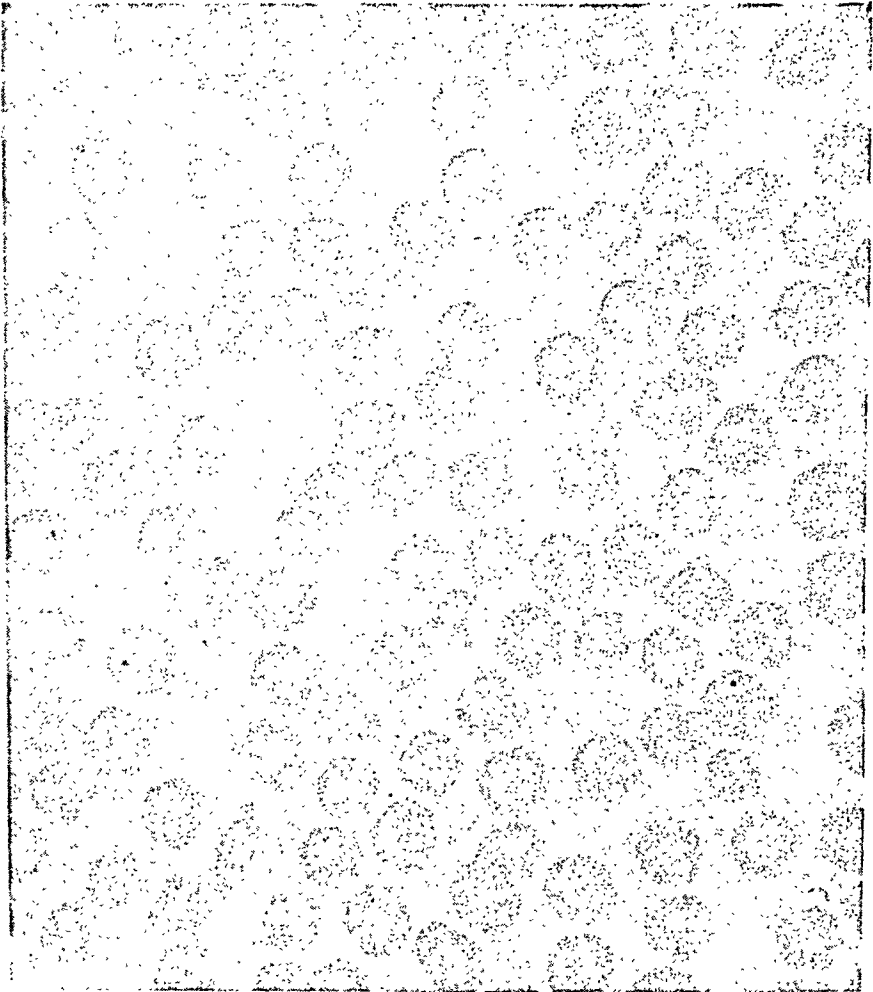


FIG. 1. Target cells and an oval cell on blood smear as seen with oil immersion.

Numerous hematological studies were made over a period of one month. The following data are average figures.

TABLE I

Hemoglobin.....	83% <sup>9*</sup>
R.B.C.....	6,300,000 per cu.mm. <sup>8</sup>
Color index.....	.66 <sup>8</sup>
Hematocrit.....	.41 <sup>3</sup>
W.B.C.....	9.0 per cu.mm. <sup>8</sup>
Differential.....	normal limits <sup>10</sup>
Fragility of R.B.C., Hemolysis begins at.....	0.42% <sup>5</sup>
Fragility of R.B.C., Hemolysis complete at.....	0.24% <sup>5</sup>
Reticulocyte count.....	3.3% <sup>4</sup>
Platelets.....	400,000 per cu.mm. <sup>3</sup>
Bleeding time.....	1 min. 15 sec.
Coagulation time.....	2 min. 45 sec.

\* Small numerals indicate number of tests performed.

Studies of 15 Wright stained blood smears revealed approximately one stippled red blood corpuscle, one to two oval cells, six to eight target cells and one to two polychromatophilic corpuscles per oil immersion field. There was a moderate degree of anisocytosis, poikilocytosis and hypochromia. A bone marrow smear prepared from a sternal aspiration showed a noticeable increase in erythroblastic activity with numerous oval cells, target cells and many stippled and polychromatophilic red blood corpuscles. Sickling traits were absent.

*Other Laboratory Data.* Urinalysis was negative for sugar and albumin with a few white blood cells per high power field in the centrifuged specimen. Serum albumin was 4.5 per cent, globulin 2.7 per cent. Sedimentation rate was 2.2 mm. per hour (Wintrobe). Urobilin plus urobilinogen excretion in the feces was 270 mg. in 24 hours and in the urine 2.33 mg. in 24 hours. Total fat in feces was 11.5 per cent. The cephalin-flocculation test was negative. The icteric index was 8. The fecal examinations were negative for occult blood. Blood lipase was 0.4 unit. Thiamine was 2.12 micrograms per 100 c.c. in the urine.<sup>4</sup> Examinations for lead in urine and blood were within normal limits.

Roentgenological studies of the gastrointestinal tract with special attention to the small bowel were negative. Roentgenograms of the long bones were negative. The skull as shown by roentgenogram was of the oxycephalic type.

*Hospital Course.* The patient remained well during his five weeks in the hospital except for his asthenia. A 15 day course of 2 grams of ferrous sulfate daily was without effect on the hemoglobin or red blood corpuscle count. A five day course with liver extract likewise had no effect on the hemoglobin, red blood cell and reticulocyte count.

### SUMMARY AND CONCLUSIONS

The first recorded case of Mediterranean target-oval cell syndrome in an adult Chinese male is reported. The criteria as postulated by Dameshek<sup>1</sup> for this condition are fulfilled in every respect except the racial factor. To quote Cooley and Lee<sup>5</sup> in their discussion of erythroblastic anemia: "We are not inclined . . . to lay great stress on the limitation of this or any other similar disease to a particular race."

We wish to express our thanks to Col. Wm. S. Culpepper, M.C., Commanding officer, for his cooperation.

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## PRIMARY ENDOTHELIOMA OF THE PLEURA: REPORT OF A CASE IN A PATIENT WITH CHRONIC LYMPHATIC LEUKEMIA \*

By THEODORE S. EVANS, M.D., F.A.C.P., MORGAN Y. SWIRSKY, M.D., and  
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THE etiology of leukemia at the present time is still not satisfactorily explained. Factors such as infection, trauma, drugs, toxins, and exposure to radioactive substances have been advanced as possible causes, and these have been thoroughly reviewed by Forkner.<sup>1</sup> More intriguing is the suggested relationship of leukemia to neoplastic diseases, and there is much evidence to support the classification of leukemias as a variety of neoplasia. This view has been championed chiefly by Babes,<sup>2</sup> Mallory,<sup>3</sup> Weber and Bode,<sup>4</sup> and others. Since 1878 the coexistence of the leukemias with other forms of neoplasia has been noted repeatedly by various investigators and has suggested to them an inter-relationship. Both Forkner<sup>5</sup> and Morrison et al.<sup>6</sup> have summarized the accepted cases in this group. A review of material presented by these and other authors fails to disclose any previous report of the association in the same individual of chronic leukemia and primary pleural endothelioma, and it is for this reason that the following material and case report are being presented.

Although in the past some have doubted the existence of such an entity as primary endothelioma of the pleura, most modern pathologists recognize such a class of tumor growth. In 1767 Lieutaud<sup>7</sup> reviewed and published a study of 3000 autopsies among which he described two cases of apparent pleural endothelioma. However, in 1870 Wagner<sup>8</sup> first recognized this pathological entity and described it as a "tubercle-like lymphadenoma." The first two cases definitely diagnosed as endothelioma of the pleura to be reported in the American literature were presented by Beggs<sup>9</sup> before the New York Pathological Society in 1890. Since that time a number of cases have been reported, but the belief still persists that this is a rare type of tumor. There is no doubt that many cases of pleural endothelioma have been overlooked because there is no characteristic clinical or roentgenographic picture. The symptoms most often suggest a chronic inflammatory disease process, thereby misleading the clinician as to the underlying malignant character of the lesion. It is a slow-growing tumor and metastases usually occur late in the course of the disease, long after the initial growth has become widely distributed over the contiguous pleural surfaces. This tumor shows an age distribution common to most neoplasms, being found most frequently in individuals in the 40-60 year age group. Goeters<sup>10</sup> has noted this type of tumor in children, but this is a rare occurrence. Hibler<sup>11</sup> described such a tumor in a child of five years. It is generally believed that males are more frequently affected than females, and Birnbaum<sup>12</sup> claimed that it occurs twice as frequently in males as in females. Either pleural sac may be the site of the initial lesion, but Dubray and Rosson<sup>13</sup> stated that the right pleural sac is more commonly involved.

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As stated previously pleural endotheliomata have no characteristic clinical picture. When involvement of the pleura is slight there may be few if any symptoms. The onset is usually gradual with the patient unaware of any symptoms except some exertional dyspnea, which soon may become progressive. Many other cases start as an acute pleurisy with intermittent intense pleuritic pains which gradually become constant and are accompanied by a non-productive cough, progressive weakness and some weight loss. Fever may be present, but in the majority of cases it is of no significance. Hemoptysis is usually absent. Physical examination of a patient with a fully-developed clinical picture reveals him to be dyspneic, orthopneic, and sometimes cyanotic. The temperature is usually normal, but the pulse and respiratory rates are elevated. The chest findings are those of pleural effusion with shifting of the mediastinum to the contralateral side, and roentgenogram merely confirms these findings. However, Doub and Jones<sup>14</sup> report that thoracentesis with air replacement of the fluid removed may reveal multiple tumor nodules on the surface of the pleura in films taken after such a procedure. Other roentgenologists feel that only thickened pleura can be seen following the production of such an artificial hydropneumothorax. Thoracentesis in itself may be of diagnostic aid. Several authors, Dubray and Rosson,<sup>13</sup> Rosenbaum, and Birnbaum<sup>12</sup> have made significant mention of the great resistance frequently encountered when the thoracentesis needle reaches the pleura and of the marked force necessary to insert the needle into the pleural cavity. The fluid in the early stages can be serous or serosanguinous, but in the usual fully-developed case it is frankly bloody. Furthermore, rapid reaccumulation of the effusion is the rule and with each tap the fluid generally becomes more bloody, so that these points, too, are of diagnostic significance. Lichtenstein<sup>15</sup> has pointed out that the dyspnea is slightly if at all relieved by thoracentesis and this is an important differential point from tuberculous pleurisy. The fluid resembles an inflammatory effusion, but malignant cells are often reported in the pathological examination. Saccone and Coblenz<sup>16</sup> do not feel that microscopic examination of the fluid is of much value, pointing out that "even clumps of cells with mitotic figures are not reliable criteria since mesothelial cells can grow and multiply in such fluids."

Once symptoms have appeared the clinical course is progressively downward with gradually increasing weakness, cachexia, and secondary anemia, symptoms all common to any advanced malignancy, plus marked dyspnea and orthopnea. Death is usually due to cardiac or respiratory failure and is often preceded by a comatose state. The duration of the illness is variable and there is no statistical agreement as to life expectancy from the onset of the first symptoms. Dubray and Rosson<sup>13</sup> give six to nine months as life expectancy, whereas Geschickter<sup>17</sup> feels that the average duration is two years. Treatment is essentially palliative, as the disease is invariably fatal.

The gross appearance of pleural endotheliomata at autopsy presents several striking features. The corresponding lung is usually completely encased and compressed by markedly thickened pleura which in some cases has measured 1 to 1.5 cm. in cross-section. In the majority of cases the greatest pleural thickening occurs at the base of the lung, especially in the diaphragmatic pleura. In the fully developed case the lung of the involved side is collapsed against the hilus and a hemothorax is present. A gristle-like sensation is obtained on transection of the abnormally thickened pleura. Inspection reveals the inner

surface of the pleura to be finely nodular in type, bearing out the impression that the process first appears as multiple nodules on the surface of the pleura which subsequently fuse. The lung parenchyma itself is usually not invaded by tumor, but frequently tumor cells do invade the septa producing nodular masses. Although metastases to the axillary and cervical lymph nodes may occur they are, nevertheless, infrequent, but metastatic involvement of the peribronchial and mediastinal nodes is a common finding. The process may also spread to the neighboring pericardium, the contralateral pleura, and through the diaphragm to the peritoneal cavity to involve the mesentery near its intestinal attachment, the appendix, liver, spleen, kidney, adrenal, and infrequently the ovaries and inguinal lymph nodes. In the case of Barrett and Elkington<sup>18</sup> the spleen was entirely surrounded by a layer of growth which bound it to the chest wall and diaphragm. On microscopic examination, the tumor growth consists of cells moderate in size, polyhedral or flat, with hyperchromatic vesicular nuclei and faint nucleoli. These cells may lie in small alveolar arrangement or in long single or multiple rows between cellular or hyaline connective tissue to which they are usually intimately adherent. An infrequent finding is hyaline corpora amylacea-like bodies which are said to be characteristic. According to Ewing<sup>19</sup> the origin of the tumor is usually referred to the cells of the subpleural lymph spaces or to the lining cells of the pleura.

#### CASE REPORT

Patient A. C. C., a 40 year old married white female, was first admitted to Ward Medical Service Grace Hospital on January 12, 1944 with a chief complaint of "leukemia" of five years' duration. She stated that six years before entry (1938) she developed an exfoliative type of skin lesion with subsequent shedding of nails and much skin, but that under the care of a local dermatologist this condition gradually receded. A few months later the condition recurred and a routine blood count revealed a red blood cell count of 4.3 millions, hemoglobin of 73 per cent, and white blood cell count of 6,100 with polymorphonuclears 44 per cent, monocytes 16 per cent, and 40 per cent unidentified cells. These latter cells were large with a single nucleus presenting many of the characteristics of the monocyte, but not definitely identified as such. Physical examination at that time revealed no abnormalities except for the skin condition. A biopsy of the skin revealed the following findings: "The epithelium is covered with stratified squamous cells and is everywhere intact. Beneath the epithelium and extending up into the papillae is a cellular infiltration of lymphocytes and large mononuclear cells. These cells present a normal appearance. No cells are seen in mitotic division. It is impossible to state that this merely represents a cellular infiltration of chronic inflammation or whether these cells are an infiltration of a monocytic leukemia. From the appearance of these cells which are well preserved such a diagnosis cannot be made. Diagnosis: Fragment of skin showing chronic inflammatory reaction."

In March 1940 the patient was again seen, after a two year lapse, complaining primarily of skin symptoms accompanied by a 14 pound weight loss and insomnia. The physical examination was essentially changed in only one respect, i.e. the lymph nodes in the cervical, axillary, and inguinal regions were enlarged to the size of a robin's egg, and the spleen was barely palpable. The red blood cell count was 5.0 millions, hemoglobin 82 per cent, but the white blood cell count was found to be 47,000 with polymorphonuclears 16 per cent, lymphocytes 72 per cent, and eosinophiles 2 per cent. Of the lymphocytic series, 50 per cent were adult lymphocytes and 22 per cent lymphoblasts. At this time the microscopic slides of the skin lesions and the blood

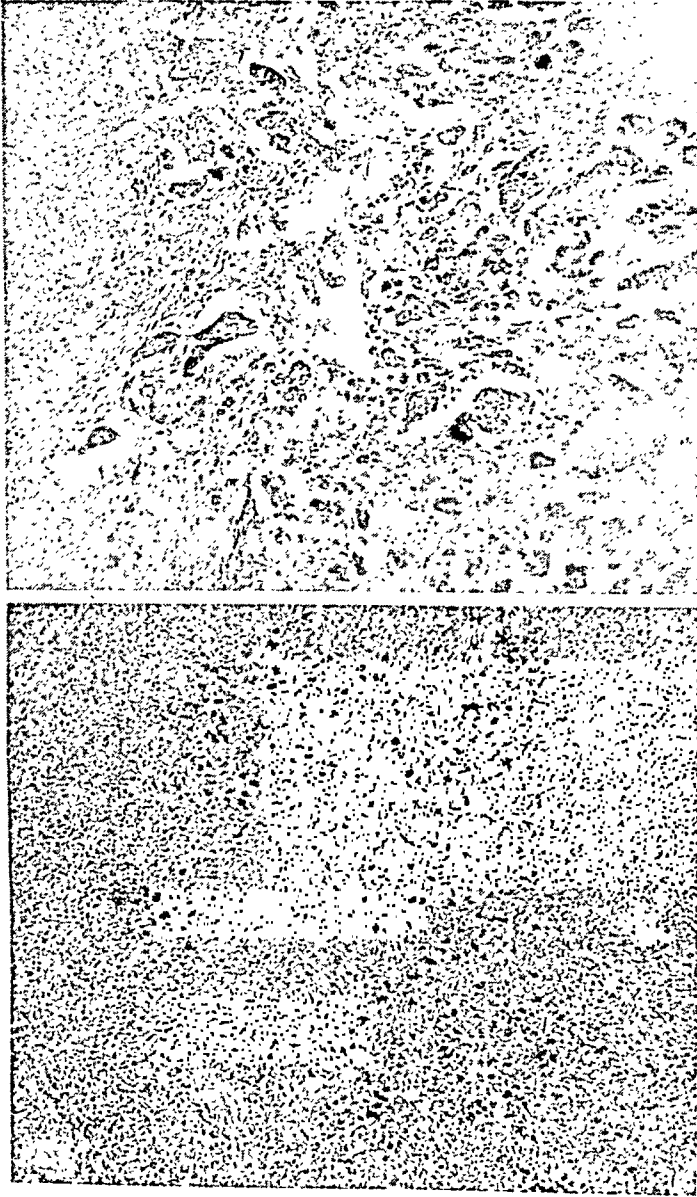


FIG. 1. Spleen: Many dark staining lymphocytes are seen in the spleen. This picture is consistent with lymphocytic leukemia.

FIG. 2. Lung: This section shows the tumor cells which have invaded the lung tissue and are arranged in groups suggesting small acini. These are polyhedral endothelial cells and in many areas under high power show mitotic figures.



smears were sent to Dr. Bruce K. Wiseman of Columbus, Ohio, who felt that the peripheral blood smears showed a definite leukemia and that the skin lesion was consistent with chronic lymphatic leukemia.

In April 1940 the patient was seen at the New Haven Hospital Radiology Department where physical examination revealed a bright-red scaling dermatitis which involved the entire body including the soles, palms, and scalp. The cervical, axillary, and inguinal lymph nodes were enlarged and the tip of the spleen was felt five fingers' breadth below the left costal margin. The legs were swollen from the knees down and showed 2-plus pitting edema. No leukemic infiltrations were noted in the fundi. A blood count showed a red blood cell count of 3.9 millions, hemoglobin of 78 per cent, and a white blood cell count of 47,000 with predominance of lymphocytes. From April 1, 1940 to May 6, 1940 she was given generalized body irradiation in nine treatments, at the conclusion of which she felt better, her white blood cell count had dropped to 18,000, but her skin condition was unimproved. In November 1940 she was again seen at that Radiology Department for the same skin condition, at which time the white blood cells numbered 47,000, so that between November 27, 1940 and December 25, 1940 she received 10 roentgen-ray treatments again with no effect on the skin condition and with a drop in the white blood cell count to 33,000. In July 1941 she returned again for a course of therapy with the skin condition at that time much worse and the white blood cells totaling 48,000. A series of eight roentgen-ray treatments was given from July 10, 1941 to July 28, 1941 which did not improve the patient's skin condition nor her general well-being, and the total white blood cell count at conclusion of therapy was 25,000.

In the fall of 1941, Dr. Charles Doan, of Columbus, Ohio, examined the patient and confirmed the diagnosis both in regard to the skin condition and the underlying leukemia. Her skin condition continued to be her chief source of discomfort, she saw several physicians and was also seen at Memorial Hospital, New York City, and all consultants stated that she had "chronic leukemia" and nothing further in therapy could be offered.

During the years 1942 and 1943 the patient received no treatment whatsoever and was not seen by any physician. However, during this period her skin condition improved greatly, and she had gained both in weight and strength. After this short period of relative well-being, she again began to get worse. For a few months before entry to the hospital she experienced frequent episodes of profound asthenia. About three days before admission, progressive exertional dyspnea and orthopnea appeared, accompanied by cough and right-sided chest pain so that medical aid was sought when respiratory distress was very marked. The past history and systemic review were non-contributory, but the family history revealed that her father died of lung cancer.

Physical examination on admission revealed a very pale dyspneic and orthopneic white female, sitting upright in bed, gasping for breath, and apparently in extremis. The pupils were equal in size and reacted well to light. No leukemic infiltrations were found in the fundi. The nasal septum was intact and no obstruction was noted. The ears, lips, mouth, and pharynx were not remarkable aside from complete edentia. A few shotty cervical lymph nodes were felt, but no other lymphadenopathy was noted. The trachea was deviated to the left. The chest showed no respiratory motion on the right side where from apex to base there was flatness to percussion, absent tactile and vocal fremitus, and absent breath sounds. The left chest was resonant to percussion and clear to auscultation with exaggerated breath sounds. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. Heart examination revealed apex beat at left anterior axillary line, regular rhythm with tachycardia, and tones of good quality with no murmurs. The abdomen was markedly distended and tense so that nothing was felt at this time. No masses were found in the breasts. There was 2-plus edema of the lower limbs, and the reflexes were sluggish. The skin was dry and scaly, and had a brawny feel over the neck, back, abdomen; and lower extremities.

An immediate right thoracentesis was performed and 3250 c.c. of blood-tinged fluid were released, examination of which revealed small groups of peculiar polyhedral cells, suggesting tumor cells, but no mitoses were found. Similar cells were found in fluid removed on the tenth and eighteenth hospital days. The initial blood count showed a red blood cell count of 3.9 millions, hemoglobin 83 per cent, and a white blood cell count of 6,500 with polymorphonuclears 72 per cent, lymphocytes 24 per cent, eosinophiles 3 per cent, and basophiles 1 per cent. Subsequent white blood cell counts revealed similar findings, and study of the sternal marrow showed it to be active in both the granulocytic and erythropoietic series, with many more monocytes present than normal. Platelets totaled 105,000 per cu. mm. The non-protein nitrogen was 25 mg. per cent, blood sugar 95 mg. per cent, uric acid 2.6 mg. per cent, and serum proteins 5.31 gm. per cent. The Wassermann and heterophile antibody reactions were negative. The sedimentation rate was rapid. The admission urine showed specific gravity 1.025, 4-plus albumin, 4-plus acetone, and numerous white blood cells and red blood cells. A chest roentgenogram taken on the day after admission revealed a well-defined right hydropneumothorax with approximately 80 per cent collapse of the right lung, which appeared to be atelectatic; displacement of the heart and mediastinum to the left, and mottling in the left lower and midlung fields. The bony thorax was normal, and a metastatic series revealed no abnormalities. A flat film of the abdomen revealed marked enlargement of the liver with the inferior margin about 3½ cm. below the crest of the ileum, and a large spleen measuring 15 cm. by 3½ cm.

Following the thoracentesis, the respiratory distress was relieved, the patient was comfortable and the abdominal distention decreased, so that the spleen and liver were palpable. A gynecological consultant found no pelvic abnormalities. She was allowed out of bed and discharged home on February 2, 1944.

Following discharge the patient felt well for five days and then had a recurrence of rapidly progressive dyspnea and orthopnea, accompanied by profound anorexia, nausea, vomiting, asthenia, and insomnia, so that hospitalization was again ordered.

The patient was readmitted to Grace Hospital on February 9, 1944. Physical examination again revealed her to be in acute respiratory distress. The right breast was larger than the left due to dependent edema. The heart was unchanged. Over the left lower lobe there was flatness to percussion with decreased tactile and vocal fremitus, and absent breath sounds at the base, while over the right lung fields the signs of a hydropneumothorax persisted. The liver extended down to the iliac crest, and the spleen was four fingers below the left costal margin. Pitting ankle edema was present. Lichenification and scaling of the skin were noted in addition to the presence of numerous red macular lesions. A left thoracentesis was done with release of 900 c.c. of serosanguinous fluid, the examination of which showed cells similar to those seen in the fluid from the right chest on the first admission, but in addition there were mitotic figures. The blood count revealed no anemia and a normal total white count of 5,800 with 17 per cent eosinophiles and 53 per cent polymorphonuclears. The eosinophilia was present in several subsequent blood counts, but was not as marked. The urine showed 1-plus albumin and scattered red blood cells and white blood cells. A repeat chest film was taken and again revealed the right hydropneumothorax with collapsed right lung, while in the left mid-lung area small mottled opacities were noted with a small left pleural effusion. Despite all supportive measures and repeated thoracenteses, the patient rapidly grew worse and died on March 1, 1944.

*Autopsy Findings.* The body was that of a fairly well-developed, undernourished, pale white female, measuring 63 inches in length. Rigor mortis was absent, but postmortem lividity was present.

On opening the abdominal cavity a somewhat larger amount than normal of peritoneal fluid was present which was clear and straw-colored. The liver was found to extend nine fingers'-breadth below the right costal margin. The dome of the dia-

phragm on the right side was at the level of the sixth rib, while on the left side it was at the level of the seventh rib. The spleen extended three fingers'-breadth below the left costal margin.

On opening the thoracic cavity the mediastinum was found to be shifted somewhat to the left, away from the midline, and fixed in this position by abnormally thick fibrous adhesions. The right pleural cavity was completely filled with bloody fluid. The left pleural cavity contained a smaller amount of bloody fluid and the pleura here was somewhat thickened. In place of the right lung was an elongated structure about 17 cm. in length which extended down to the diaphragm with which it became incorporated. At the lower part just above the diaphragm this measured about 4 cm. transversely and higher up about 7 cm. It was about 4 cm. thick. It consisted of firm white tissue apparently representing the tremendously thickened pleura, and in the center of this mass was the remains of the compressed right lung. The peribronchial lymph nodes were somewhat enlarged and quite hard. On section of this compressed lung, no tumor growth was found in the lung tissue except small lymph nodes which appeared to be involved. The left lung showed collapse of the lower half of the lower lobe, and there were some grayish nodules attached to the pleura here. The upper lobe was fairly well-expanded.

The diaphragm was very much thickened, most markedly on the right side, where it measured as much as 12 mm. in thickness. A thin muscle layer could be recognized in the center of this, but on both surfaces there was compact grayish tissue. This was particularly hard on the undersurface of the diaphragm.

The heart weighed 265 grams. The pericardial fluid was somewhat increased in amount and was blood-tinged. The superficial vessels were somewhat tortuous, showing that the heart had been larger. The orifices were of normal size. One cusp of the mitral valve showed some grayish thickening. The myocardium showed nothing of particular note. The coronary arteries were smooth.

The spleen weighed 315 grams. It was smooth on the surface, and the capsule was not thickened. On section it was moderately firm and showed considerably enlarged malpighian bodies, a picture which would be consistent with lymphatic leukemia.

Gastrointestinal tract. Near the cecum there was a mass of firm adhesions binding the intestines together, and there was here a very firm area attached to the retroperitoneal tissue. The stomach showed nothing of particular note. Along the course of the small intestine there were minute hard nodules at the mesenteric attachment. The appendix was present. Very near the attached end of the appendix was the firm tissue described above, which on section suggested the possibility of a small tumor. This did not involve the mucous membrane in the gross. No tumors of the mucous membrane were found.

The pancreas appeared normal.

The liver weighed 1,570 grams. It was smooth on the surface with some thickening of its capsule on its anterior surface. On section the liver showed no definite abnormality. No tumor nodules were found in it. No calculi were present in the gall-bladder.

The adrenal glands showed nothing of particular note.

Kidneys: Combined weight 240 grams. Capsules stripped a little less readily than normal, but left a smooth surface. The cortex was rather pale and somewhat thinner than normal. The pelvis of the right kidney was a little dilated.

A few somewhat enlarged lymph nodes were found in the abdomen.

The abdominal aorta and its main branches showed no arteriosclerosis.

The uterus was small and showed nothing of note. The ovaries had some small cysts and one of them had a small solid grayish nodule suggesting tumor growth. The bladder was apparently normal.

*Anatomical Diagnosis.* Marked chronic thickening of pleura with encasing of right lung. Bilateral hemothorax. Partial atelectasis of left lower lobe. Chronic thickening of diaphragm. Old peritoneal adhesions with questionable tumor. Numerous small retroperitoneal nodules attached to the intestine. Moderate enlargement of the spleen with hypertrophy of the malpighian bodies. A few enlarged lymph nodes.

From the gross findings the one thing which suggested lymphatic leukemia was the appearance of the spleen. The condition in the chest and the diaphragm, and the firm peritoneal adhesions were difficult to explain on this basis as their etiology was not evident from these gross findings.

*Microscopic Examination.* A malignant tumor growth was found in the thickened pleura of the right lung, in the small nodules in the pleura of the collapsed lower lobe of the left lung, peribronchial lymph nodes, the diaphragm, the adhesion of the cecum near the appendix, the minute nodules in the mesentery of the small intestine, the retroperitoneal lymph nodes, and the ovary. The type of tumor was apparently the same in all these locations. As seen in the thickened pleura of the right side, the tumor growth showed spaces lined with cells with much compact fibrous tissue between these spaces. The cells lining these spaces varied in shape, some being quite flat, but others were cuboidal and approaching the columnar type. To this extent they resembled a glandular growth. Where the cells of the tumor were more numerous, as in the lymph nodes, there was no definite arrangement. From the appearance of the cells of the tumors, the classification is difficult. The possibility of a malignant carcinoid was considered and a section was stained by the argentaffin method with negative results. From the distribution of this tumor growth, involving as it evidently had for a long time the right pleura and diaphragm, it seems most probable that this was primary in the right pleura, and is an endothelioma. It was evidently slow growing as shown by the large amount of compact fibrous tissue in the right pleura and diaphragm. In sections of the right lung, minute areas of tumor were found in the lung tissue, but these in all probability were metastatic and the growth was not primary here. In sections of the proximal end of the appendix and adjacent tissue, the tumor growth was found extending up to the outer part of the mucous membrane. Although it is a most unusual picture, in my opinion, as given above, it is an endothelioma.

The heart showed no definite abnormality.

*Lungs:* In addition to the tumor growth, the right lung was much collapsed as was also the lower lobe of the left lung. Sections of the left upper lobe showed air spaces better expanded, but with numerous pigment-containing cells resembling heart-failure cells.

The spleen showed large malpighian bodies with a considerable number of small round cells in the stroma between these.

The pancreas showed no definite abnormality.

*Liver:* Nothing suggesting tumor growth was seen, and there was no collection of lymphocytes between the columns of liver cells.

*Kidneys:* In some fields there were numerous small cells, but these had the appearance of developing connective tissue cells and not lymphocytes. In most areas these cells were lacking.

*Skin:* Sections showed some small groups of round cells under the epithelium, indicating a chronic inflammatory process here.

*Bone Marrow:* Sections of a rib showed normally active marrow.

Regarding the presence of any lesions indicating lymphatic leukemia, the appearance of the spleen would be consistent with, but not diagnostic of this condition. The other organs, particularly the liver and kidney, did not show the lymphocytes one expects to find in that disease.—Dr. Charles J. Bartlett, Pathologist, Grace Hospital, New Haven, Connecticut.

## DISCUSSION

The case recorded above is by all available criteria typical of a pleural endothelioma from both the clinical and pathological standpoints. The symptomatology and physical findings were classical for a fully-developed case. The initial thoracentesis gave transient relief of the dyspnea and orthopnea, but rapid reaccumulation of the fluid took place and subsequent chest taps provided little or no palliation. The fluid was always hemorrhagic and on several occasions mitotic figures were present on microscopic examination of the sediment, suggesting tumor cells. Thoracentesis was difficult owing to marked pleural thickening. Roentgenographic examination of the chest following the creation of an artificial pneumothorax revealed no evidence of pleural tumor nodules, but did show the atelectasis of the right lung and the shifted mediastinum.

In the contralateral lung several areas of mottling were found on roentgenogram which at autopsy proved to be tumor nodules in the lung septa. Careful examination of the lungs and bronchi failed to reveal evidence of bronchogenic carcinoma. The terminal picture is primarily due to the pleural endothelioma with widespread metastases rather than to the underlying leukemic condition, as the only evidence remaining at autopsy of her previous leukemia was the presence of enlarged malpighian corpuscles in the spleen.

The original complaint for which the patient consulted her physician was a chronic exfoliative dermatitis which some time after its onset was accompanied by a marked leukocytosis, the differential count showing a marked predominance of lymphocytes and lymphoblasts. At first it might appear that the patient had a primary skin disease with an associated leukemoid reaction. However, the clinical course during the next few years with marked generalized adenopathy, splenomegaly, and persistently elevated white blood cell counts with predominance of lymphocytes and lymphoblasts rules against such a supposition. Furthermore, the diagnosis of leukemia was confirmed by Drs. Charles Doan and Bruce Wiseman of Columbus, Ohio, by Dr. C. P. Rhoads of Memorial Hospital, New York City, and at the New Haven Hospital Out-Patient Department. A leukemoid reaction in association with neoplasm has been reported by several authors<sup>20, 21, 22, 23, 24, 25</sup>; however, this condition occurs when metastases are present in the bone marrow and spleen and is usually a terminal event.

Because of the duration of this patient's illness following the onset of her elevated white blood count it is inconceivable that this represents a leukemoid reaction to a neoplasm since statistics show that life expectancy in patients with pleural endothelioma is two years or less on the average. Furthermore, the presence of a normal sternal marrow and peripheral blood smears at her last admission rules against metastatic bone marrow involvement. At autopsy the spleen did not show metastatic involvement, but rather findings consistent with lymphatic leukemia.

The most intriguing point in this case aside from the association of a rare neoplasm with leukemia is the paucity of evidence of chronic lymphatic leukemia at autopsy. Forkner<sup>1</sup> has stated that in a small proportion of patients with chronic leukemia temporary improvement may occur for weeks or months, whereby the leukocyte count may be reduced and organs decrease in size, these changes being independent of any particular form of treatment. Such reactions would appear to represent possible spontaneous remissions. Furthermore, in

some cases following roentgen-ray therapy a definite decrease in the white blood count and in liver, spleen, and lymph node enlargement does occur. A few authors<sup>26, 27, 28, 29</sup> have observed spontaneous remissions in untreated cases, but no examples of anything approaching complete spontaneous remission of chronic leukemia has been recorded, although Doan and Wiseman<sup>30</sup> and others have reported that patients with chronic lymphatic leukemia may live many years and die of totally unrelated causes. Numerous authors, Minot and Isaacs,<sup>31</sup> Arendt and Gloor,<sup>32</sup> and others have reported improvement and even moderate remissions in patients treated with roentgenogram. It would appear, however, in our case either that roentgen-ray therapy produced an unusually long remission with disappearance of the characteristic clinical-pathological findings, or else a true prolonged spontaneous remission occurred, either of which is indeed extremely unusual.

If one subscribes to the point of view that leukemias are neoplastic in origin and that occurrence of a second neoplasm, not metastatic, frequently inhibits the growth of the first one, then it is also not inconceivable that the leukemic remission in this case was caused by such a mechanism.

### SUMMARY

A case of primary endothelioma of the pleura with widespread metastases in a patient with chronic lymphatic leukemia is reported.

The pathology, clinical course, and roentgenographic findings of pleural endothelioma are reviewed.

The leukemic picture in our patient antedated the malignant process in the pleura and apparently played no part in the terminal picture, as is evidenced by the paucity of lesions of lymphatic leukemia at autopsy.

The possibility that irradiation therapy had produced a prolonged remission in the leukemic state is discussed.

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## FRIEDLÄNDER'S BACILLUS MENINGITIS WITH REPORT OF CASE TREATED UNSUCCESSFULLY WITH SULFADIAZINE\*

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MENINGITIS due to Friedländer's bacillus, a rare medical entity, was first described with a reported case by Weichselbaum<sup>1</sup> in 1888, six years after Friedländer's original description of the organism. In 1931, Rothschild<sup>2</sup> found in the American literature only a single case of Friedländer's meningitis and this one ended fatally.<sup>3</sup> Rothschild's case, the second American case reported, according

\* Received for publication December 14, 1944.

to Ransmeier and Major<sup>4</sup> is the only incontestable non-fatal case, prior to sulfonamide therapy, of purulent meningitis in which Friedländer's bacillus was recovered from the spinal fluid and adequate details of its bacteriologic identification given. Recovery in this case followed adequate surgical drainage of a subdural abscess secondary to bilateral otitis media and mastoiditis. Commenting on Carcelli's<sup>5</sup> review of 12 cases in the literature with three reported recoveries, Rothschild<sup>2</sup> found that in the recovered cases the bacteriologic diagnosis was not satisfactorily confirmed.

MacKay,<sup>6</sup> quoting Neal's<sup>7</sup> statistics, found six cases of meningitis due to Friedländer's bacillus in 3599 cases of meningitis in the New York area. Finland and Dingle,<sup>8</sup> writing in the Medical Progress series on treatment of meningitis, list one reference<sup>15</sup> of Friedländer's bacillus meningitis, a case which recovered with sulfapyridine. Yaskin<sup>9</sup> studied meningitis as a complication of nasal or aural disease and found that 58 of 123 cases of meningitis in general hospital practice originated as a complication to nasal or aural disease. Staphylococcus, pneumococcus and streptococcus predominated and the one case of Friedländer's bacillus meningitis listed was of systemic rather than of nasal or aural origin.

MacKay and Morris,<sup>10</sup> reported a case of bacillus Friedländer meningitis secondary to prostatic suppuration. Localization of Friedländer's bacillus infection in 198 cases as studied by Baehr, Schwartzman and Greenspan<sup>11</sup> is disclosed in the following table.

Gastrointestinal tract .....	30%
Genitourinary tract .....	25%
Biliary .....	23%
Lungs and upper respiratory tract .....	12%
Muscle, skin and meninges .....	5%
Vagina, uterus .....	3%

In 1942 Ransmeier and Major,<sup>4</sup> in reporting their case and reviewing the available literature, were able to collect data on but 30 cases of meningitis caused by encapsulated bacilli of the Friedländer group. Four of these reports are from the United States,<sup>2, 12, 13, 14</sup> one from Canada,<sup>15</sup> and one from Cuba,<sup>16</sup> and the rest from European journals (see 4 for references). Their summary well characterizes the Friedländer bacillus meningitis. The disease occurs chiefly in infants and in adults, often after the fourth decade. A primary focus, as determined by the recovery of the Friedländer bacillus there simultaneously with its recovery from the spinal fluid, was present in the middle ear, mastoid and sinuses in over half the adults while in the majority under three years a primary focus was undetermined. Pneumonia was a precursor in five cases. Cholecystitis, arthritis, uterine infection and pharyngitis are mentioned. Elsewhere prostatic suppuration is mentioned.<sup>10</sup> Six of the adults had diabetes, one cirrhosis of liver, others were alcoholics, two infants had congenital syphilis and two had intracranial hemorrhage—all of which suggested that debilitating conditions may predispose to the development of Friedländer's bacillus meningitis. The diagnosis is dependent upon finding in the smear and in the cultures of the spinal fluid the organisms fitting the description of Friedländer's bacillus. Friedländer's bacillus meningitis simulates that due to the meningococcus in its tendency to the development of petechiae and the likely absence of organisms on direct smear of the spinal fluid. Five of 19 cases had negative direct smears. Culture of the



first spinal fluid was positive in 15 of 17 cases. The fluid has the characteristics of a purulent meningitis with many polymorphonuclear leukocytes present, increased protein and low sugar. Of 10 cases having blood cultures, five were positive and all died. Of five with negative blood cultures two survived.<sup>15, 2</sup> Prior to the advent of the sulfonamides, meningitis due to the Friedländer bacillus (with one exception<sup>2</sup>) was invariably fatal; since then four cases are reported as cured, two with sulfapyridine<sup>15, 16</sup> and two with sulfadiazine.<sup>17, 18</sup> Sulfapyridine is, therefore, somewhat effective but sulfadiazine is the drug of choice in the treatment of Friedländer bacillus meningitis.<sup>19, 20, 13</sup>

Principally because of the rarity of the above described medical entity—formerly considered invariably fatal but now with some hope of cure with sulfonamide therapy—I present the clinical and pathological details of the following case which failed to recover with sulfadiazine therapy, and in which the precise bacteriological diagnosis was made post mortem.

#### CASE REPORT

This six month old white infant was first brought to my office August 14, 1944 because of an illness of several days characterized primarily by diarrhea but also by vomiting, cough, fever and irritability. Two days earlier a physician elsewhere had given the baby medication for the diarrhea but without improvement. History disclosed that the patient, although somewhat pale from birth, had never been significantly ill. He had developed and grown normally from all appearances. He had been delivered elsewhere at term by an elective Caesarean section, seven days after which the mother died, apparently of intestinal obstruction. This baby was from the sixth pregnancy. Offspring one, two and four were living and well whereas number three died shortly after birth from spina bifida and number five died at three months of pertussis. Physical examination disclosed an acutely ill, lethargic, pale infant with rapid pulse, respirations of 50 to 60, and a rectal temperature of 104° F. There was moderate mucopurulent nasal discharge, negative ear drums, moderately infected throat with slightly dry mucous membranes. There were scattered râles in the lungs, especially in the lower right lung. The abdomen was neither distended nor tender. The neck was not stiff, and there was no Kernig reaction. A diagnosis of a respiratory infection, probably pneumonia, was made, and the gastrointestinal picture was considered as a secondary manifestation.

Inasmuch as the infant had not vomited for over 24 hours, it seemed that oral fluids and medication would be satisfactorily tolerated. The following orders were given: 1. Diet as tolerated of equal parts of boiled milk and water. 2. Sulfadiazine, 0.5 gram at once, 0.25 gram in one hour and thereafter 0.25 gram every four hours, crushed and mixed with teaspoonful of Karo syrup. 3. A tablet consisting of 0.015 gram of phenacetin and 0.060 gram of acetylsalicylic acid was to be given every three to five hours as needed for restlessness. Twenty-four hours later it was found that the above orders were carried out uneventfully but without improvement, especially of the diarrhea, which seemed of greatest concern to the attendants. Temperature was 103° F. rectally. Sulfadiazine was increased to 0.5 gram every four hours. After another 24 hours, now 48 in all with adequate sulfadiazine clinically, there was still no apparent improvement. (There was no practical method available in this rural situation to determine whether the blood level of sulfadiazine was adequate, but the above doses, checked by counting tablets, were given and the baby, by report, had not vomited during this time.) The baby, now for the first time, refused oral medication and nourishment. He seemed more lethargic, with suggestive stiffness of the neck and with depressed fontanelles, all of which were considered mani-

festations of further dehydration and he was hospitalized forthwith, primarily to restore the fluid balance and for whatever other treatment seemed indicated.

The infant promptly went into coma with temperature 102.6° rectally, pulse 160, and respirations 60. The left side of the body seemed more rigid than the right. The neck was moderately stiff. The signs in the lungs were unchanged. Respiratory distress, including cyanosis, was not as significant as the gravity of the general picture presumably from a complicating meningitis.

Laboratory examination showed the urine to be acid, straw colored, with cloudy test for albumin, negative test for sugar and urates and epithelial cells in the sediment. There was a trace of acetone. Red cell count was 4,180,000 with 52 per cent hemoglobin. White cell count was 53,600 with 64 per cent polymorphonuclear leukocytes, 6 per cent myelocytes, 20 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophiles. By spinal puncture, only about 2 c.c. of blood were obtained. (It is unlikely that the spinal canal was penetrated.)

Following the administration of 1,000 c.c. of normal saline solution by hypodermoclysis in two 500 c.c. doses over a period of 36 hours, the infant developed generalized edema, particularly evident in the facies and in the scrotum. Twelve hours before death, a Levene stomach tube was passed. The fasting contents of the stomach had a sticky grayish green appearance but they were not studied microscopically. Along with three ounces of boiled water 1.0 gram of sulfadiazine in a single dose was administered. Also, the formula, in two ounce quantities, was given twice before a recurrence of vomiting occurred. The patient's temperature was between 98° and 99° F. during the last 36 hours, but there was very little change in pulse and respirations. Oxygen was not given, inasmuch as the small degree of cyanosis as well as the but slight to moderate respiratory difficulty seemed less significant than the dehydration and infection. There was no diarrhea throughout the hospital stay of three and one-half days. Six days after I first saw the infant and after at least 10 days of illness treated as outlined, the patient died. Clinical diagnosis was pneumonia complicated by meningitis with the causative organism undetermined before death.

*Autopsy Findings.* The autopsy findings of importance were bilateral bronchopneumonia, catarrhal ileocolitis with gaseous distention of the entire gastrointestinal tract, lymphoid hyperplasia of the spleen, cloudy swelling of the liver and kidneys, and diffuse lepto-meningitis. Cultures taken from the subarachnoid fluid, the heart's blood and the contents of the ileum showed a gram negative bacillus having the cultural characteristics of Friedländer's bacillus.

The pathologist\* wrote: "In reviewing the history, it is my opinion that the enteritis previous to the present illness probably was the predisposing factor in the onset of the terminal disease. Although Friedländer's bacillus is occasionally found in the intestinal tract as a pathogen, it is more commonly found in the respiratory tract and, in view of the fact that a well established bronchopneumonia was found in both lungs, I believe that the pneumonia, the bacteremia and the lepto-meningitis were the result of a complicating secondary infection terminating fatally. It would be fair to assume that the primary infection with the Friedländer organism probably occurred in the lungs. The changes in the heart, liver, spleen and kidneys are secondary to the toxemia of infection."

*Bacteriological Findings.* Cultures taken from the small bowel, heart's blood and subarachnoid fluid revealed a gram negative bacillus having the cultural and morphological characteristics of Friedländer's bacillus, as verified by the State Department of Health laboratories.†

The bacteriological findings were gram negative, encapsulated diplo-bacilli which grew at room temperature, at 37° C., aerobically and under slightly decreased oxygen

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† Director, Division of Diagnostic Laboratories: Laura G. Jacques, M.D., Concord, New Hampshire.

tension on a variety of media including Loeffler's blood serum, blood agar, dextrose agar and in broth. On solid media the colonies were moist, confluent and blue gray. The organism fermented dextrose, sucrose and lactose. Although it is not of differential diagnostic importance the organism also fermented maltose and mannitol. A guinea pig injected intraperitoneally, with a 24 hour culture, died within 18 hours. The peritoneal exudate was stringy and the organism recovered morphologically resembled the one introduced into the peritoneum.

### SUMMARY

Friedländer's bacillus meningitis as reported, particularly in the American literature, is exceedingly rare. It has a predilection to occur in infants and in adults past middle age. Although formerly considered invariably fatal, meningitis due to Friedländer's bacillus in recent years has occasionally been cured with sulfapyridine or sulfadiazine, the latter being the more effective. The case report of this paper is of an infant treated adequately clinically with sulfadiazine but without success. Autopsy studies confirmed the diagnoses of bronchopneumonia, ileocolitis and meningitis with the causative organism proved to be the Friedländer bacillus.

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## APLASTIC ANEMIA FOLLOWING EXPOSURE TO PRODUCTS OF THE SULFITE PULP INDUSTRY: A REPORT OF ONE CASE \*

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THIS case presents many features of interest. The disease is uncommon and rarely seen by the general practitioner. No report in the literature has been found in which a case of aplastic anemia may have been caused by exposure to products of the sulfite pulp industry. The history revealed that symptoms of intoxication were present for some 17 months prior to seeking medical aid.

The patient for some 20 years was manager of a pulp and paper company which makes paper pulp by the Mitscherlich or sulfite process, in which wood chips and calcium bisulfite enter large digesters or autoclaves and emerge finally as sulfite pulp. He was almost daily exposed to fumes at times of high concentration in closed areas and was constantly handling and frequently seen chewing pieces of sulfite pulp.

Many industrial studies have been made of the toxicological effects of the more commonly used chemicals. Such studies will not of necessity apply directly to the paper industry in which the contaminating chemical substances are not clearly identified and the actual amounts of toxic constituents may be so small as to be estimated with difficulty.

Among the possible toxic materials in a sulfite pulp mill are the relief gases from the digester. Investigations of the oil soluble constituents of relief liquor from the pulp mill have revealed some interesting findings. The oil-soluble fraction in relief liquor represents about 4.5 parts in 12,000, of which about 90 per cent is para cymene. Cymene is a substituted benzene and as such is an irritant. According to Woronow (1929),<sup>1</sup> cymene closely resembles pseudo cumene in its effects, and it does not exhibit the tendency, shown by benzene to cause anemia and leukopenia; similar results were reported by Miyamoto (1937).<sup>2</sup> Cymene (cymol), methyl isopropyl benzene, can exist in the form of three isomers, of which only the para compound has been studied toxicologically. Other constituents of relief liquor are: sulfur dioxide gas, acetaldehyde, acetone,

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methyl alcohol, acetic acid, formic acid and terpenes. Of these constituents, aside from benzene, acetone has been found after continued inhalation to cause a destruction of the red cells and hemoglobin, and may produce chronic tissue damage in high concentrations. These irritants either singly or in combination were probably important etiological factors in this case. The effect of cymene and the other related terpene derivatives in the exhaust gases from the sulfite industry has not been demonstrated.

The effects of benzene poisoning have been extensively studied. The following recent articles contain points of special interest.

Hunter<sup>3</sup> reported a study of 89 individuals exposed to benzene fumes and said that marked variations in individual susceptibility exist and suffice to explain why in the same concentration of fumes one individual is poisoned and another is not. According to his observations the first clinical symptoms and signs of chronic poisoning may appear long after exposure has ceased. Selling and Osgood<sup>4</sup> collected from the literature 54 cases of aplastic anemia in whom symptoms developed from two weeks to 35 years after exposure. The average was one year or less. Hunter<sup>3</sup> observed that benzene may bring about: polycythemia or anemia; leukocytosis or leukopenia; leukemia or leukemoid blood pictures (either lymphatic or myeloid); eosinophilia; megalocytosis or microcytosis; the presence of immature marrow elements in an otherwise normal blood. This author questions whether any concentration of benzene greater than zero is safe over a long period of time.

Greenburg et al.<sup>5</sup> report that the symptoms of early benzene poisoning, such as weakness, fatigue, epistaxis, dryness of the throat, loss of appetite, nausea, dizziness, insomnia, lethargy and dermatitis, may or may not be present in persons with serious blood changes, characteristic of benzene intoxication.

It seems probable that many cases of intoxication occur in the paper industry but are not recognized.

#### CASE REPORT

*History.* C. K. B., a white male aged 56 years entered St. Elizabeth Hospital, Appleton, Wisconsin, on December 5, 1942. He had been in good health until July 1941 when he began complaining of progressive weakness and lassitude. He noticed a palpitation of his heart and dyspnea upon any exertion. He especially noticed that any bump would produce bluish areas on his skin. At intervals a slight epistaxis was present coming from the left nostril. There was no history of any acute infection or sore mouth, no intake of drugs and no dietary deficiency.

The past history was negative for any hemorrhagic phenomena except the areas of ecchymosis when he bumped himself. There was no family history of blood dyscrasia, and the history was otherwise negative.

Physical examination upon admission revealed a well developed and well nourished middle aged male who did not appear acutely ill. There was a marked pallor of the skin. The temperature was 99.2° F., pulse 72, respirations 20, and the blood pressure 140 mm. Hg systolic and 90 mm. diastolic. There was present a soft diastolic murmur in the auscultation area of the aortic valve which was presumably a result of the severe anemia. Worthy of note was the absence of splenomegaly, lymphadenopathy, and absence of any internal bleeding. The examination of the prostate was negative and the roentgenogram of the pelvic bones showed no malignancy. Scattered over the palate and lower extremities were numerous petechiae of varying sizes. Areas of ecchymosis were present over the left arm and right upper eyelid, the latter

coming from rubbing his eye. No evidence of stomatitis or hemorrhages under the finger nails was present.

*Laboratory Findings.* The urine was negative except for an occasional erythrocyte and leukocyte. The stool examination was negative for macroscopic or microscopic blood.

The non-protein nitrogen was 31.6 mg. per cent, blood sugar 100 mg. per cent. The Kahn reaction was negative. Roentgenograms of the chest and the gastrointestinal series were negative. The result of the fractional test meal was as follows: The first 15 minutes, free HCl 0°. In 30 minutes free HCl 0°. Histamine 1 c.c. was

TABLE I  
Transfusions and Results of Blood Examinations

Illness Day	Amt. of transfusion c.c.	R.B.C.	Hgb. % grams	W.B.C. Total	Reticulo-cytes	Polys %	Lymphocytes %	Platelets	Hemorrhage	Bleeding Time Min.	Clotting Time Min.	Comment
1	500	1.6	4.5	1,450	0.5	34	81	638	+			
2												
3		1.9	7.1	2,200		41	58		+			
4												
5	500											
6												
7												
8		2.6	7.3	2,500		24	76		+	0	6	
9												
10												
11		2.1	6.9	1,800		23	75		+			
12	500											
13												
14												
15												
16												
17		2.9	10	2,000		12	84		++			
18	500											
19		3.7	10	1,700		16	84		++			
20+												
34-		2.4	7.6	1,100		24	76		++			
35	500	3.2	8.4	2,200	0.7	20	79	1,700	++			
36												
37		3.2	9.4	1,800		12	86		++			
38												
39												
40												
41	500	3.0	8.4	1,100		22	78		+			
42												
43		2.6	8.0	1,500		9	91		+			
44												
45												
46												
47	500								++			
48												
49++												
50		2.08	9.6	1,600	0.6	16	76	0		0 - ½ hr.		
51												
52												
53					0.2							
54					0.2							
55		3.45	10.6	1,000	0.5			70,000				
56												
57												
58		3.04	10.2	2,400	0.2			289,000				
59					0.2			153,000				
60		3.18						25,000			5	No clot retraction in 24 hrs.
61												
62		3.00		1,000				11,000				
63												
64												
65		2.56		900				12,000				
66												
67		3.37		1,200								
68												Eight transfusions of 500 c.c. given 49th to 67th day.

+ Day of discharge from hospital.  
- Returned to hospital.  
++ To Mayo Clinic.

given. In 45 minutes free HCl 0°. In 60 minutes 11° combined and total acid 22°.

Petechiae became evident on application of the blood pressure cuff for five minutes at 120 mm. of mercury.

Laboratory studies were important in establishing the diagnosis. The results of the examinations of the blood and bone marrow are given in table 1 and figures 1 and 2.

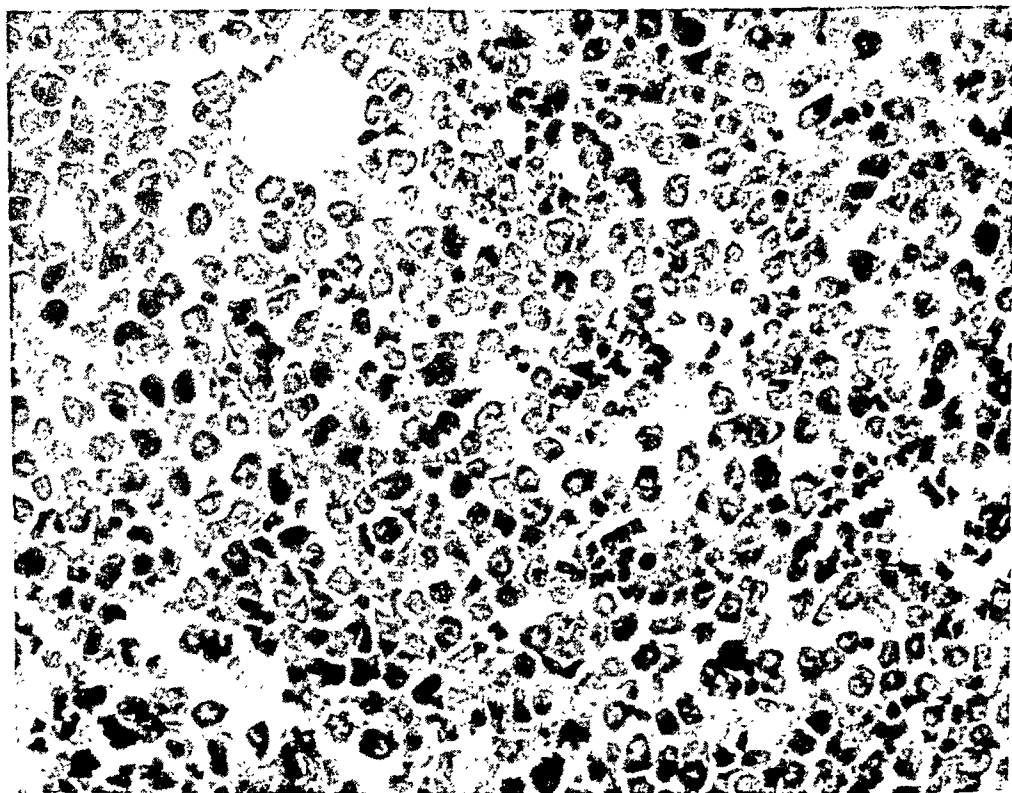


Fig. 1. Bone marrow (vertebral): The sinusoids are widely dilated and filled with normoblasts, erythroblasts, and stem cells. The marrow fat has disappeared. (500  $\times$ .)

*Clinical Course.* The patient's condition varied but little. He was placed on strict bed rest and during his stay in the hospital seven blood transfusions by the citrate method were given. The medication consisted of ample doses of liver extract, ferrous sulfate and Armour's yellow bone marrow. The diet was high in protein with added vitamin C and orange juice to insure adequate vitamin intake.

The symptoms during his stay in the hospital were those principally of an active progressive anemia with a marked lowering of all the blood elements. Bruises at the site of slight bumps and spontaneous petechiae were present. Only minor areas of infection were present in the mouth. In spite of repeated transfusions the blood showed a downward trend. After his admission to the Mayo Clinic he was given eight additional blood transfusions but gradually grew weaker, hemorrhagic phenomena became more marked including bleeding from the gums and nose and from the urinary tract, and finally, necrotic ulcers appeared on the buccal mucous membranes, tongue and throat. Sulfathiazole powder failed to control the progress of the areas treated. The throat lesion gradually grew more extensive and swallowing became difficult. He died of a cerebral hemorrhage.

*Necropsy.* On external examination the body was extremely pale. There were many petechiae and ecchymoses measuring from pin point size to 2 cm. in diameter scattered over the body, particularly along the parasternal line and the left costal margin, the upper thighs and the antecubital spaces. There was a larger ecchymosis measuring 3 by 3 cm. over the lateral aspect of the left gluteal region. No edema, jaundice or emaciation was noted.

The peritoneal cavity contained 300 c.c. of straw colored fluid. The intestinal coils were free. The liver margin was flush with the right costal margin in the mid-

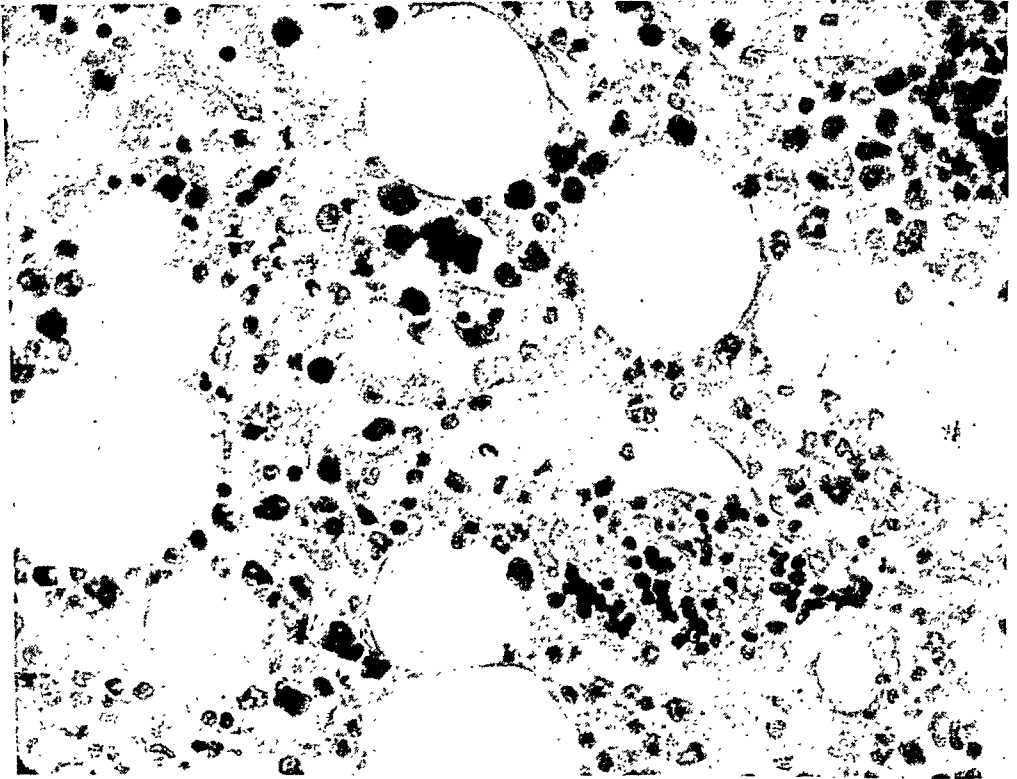


FIG. 2. Bone marrow (sternum): The fat has greatly disappeared. The marrow is scant. Numerous normoblasts and erythroblasts are present. A few maturing late normoblasts are present. (500  $\times$ .)

clavicular line and was 2 cm. above the xiphoid in the midline. The right pleural cavity contained 100 c.c. of clear, straw colored fluid, and the left pleural cavity contained 50 c.c. of a similar fluid. There were no adhesions.

The thymus was grossly replaced by adipose connective tissue. Throughout this fat were many petechial hemorrhages.

The heart weighed 449 gm., and was pinkish brown in color with epicardial fat increased grade 1. Over the surface of the heart there were numerous petechiae from pin point to 1.5 mm. under the visceral pericardium. There was a soldier's spot measuring 2 by 0.9 cm. at the base of the right ventricle posteriorly. There was no streaking.

The appendages and valves appeared normal. There was a 2 mm. petechial hemorrhage on the ventricular aspect of the left ventricular wall which on section of the septum was also seen penetrating at least 0.6 cm. The foramen ovale was closed. Coronary sclerosis was graded 1 plus. No thrombi were present.



The cardiac measurements were: aortic valve 7.4 cm., mitral valve 10.5 cm., tricuspid valve 11.5 cm., pulmonic valve 7.2 cm., depth of left ventricle 7.8 cm., thickness of left ventricle 1.4 cm., depth of right ventricle 9 cm., and thickness of right ventricle 0.3 cm.

The upper lobe of the right lung was pink in color with anthracosis grade 1, apical scarring grade 1 and no atelectasis. Consistency, crepitation, frothing and vessels appeared normal. No edema was noted. The color of the cut surface was pink. Throughout the substance and subpleural aspect of the lung and beneath the mucosa of the bronchi were numerous pin point to 1 mm. petechiae. The right middle lobe answered essentially the same description. The right lower lobe was also similar to the right upper lobe, except that the consistency was increased grade 1 and crepitation decreased grade 1. There was a 2 cm. fresh hemorrhage in the right lower lobe on the anterior aspect near the interlobar fissure. The lobes of the left lung answered essentially the same description. There was no Ghon complex nor calcified hilar nodes present.

The spleen weighed 149 gm. and was slate gray in color with grade 1 lobulations and normal consistency. Wrinkling, trabeculae and scrapings appeared normal. There was no perisplenitis. The cut surface was red. Follicles were increased grade 2. There were two accessory spleens measuring 0.9 cm. and 0.4 cm. respectively, and situated in the tissue surrounding the tail of the pancreas.

The liver weighed 1909 gm., and was reddish brown. There were two 4 cm. diaphragmatic grooves on the upper surface of the right half of the liver. The consistency was normal. The cut surface was brown, and the markings were distinct.

The gall-bladder contained 10 c.c. of greenish bile. The wall measured 0.1 cm. in thickness, and cholesterosis grade 2 was present. There were no stones.

The bile ducts were patent and not dilated.

The esophagus appeared normal. The stomach was estimated to contain 200 c.c. of gas and blackish, bloody material. The rugae appeared normal. Throughout the mucous membrane there were diffuse, scattered, petechial hemorrhages. No ulcer was seen. The pylorus was competent. The contents of the duodenum were light yellow in color. The mucous membrane appeared normal, and no ulcer was present. The A.P. distance was 7.5 cm. Throughout the small and large bowel there were hundreds of petechiae and ecchymoses measuring up to 1 cm. in greatest diameter. There were two polyps at the splenic flexure. One of these polyps measured 0.5 cm. and had a 0.2 cm. pedicle. The other one was sessile and measured 0.5 cm. in diameter. There was melanosis of the cecum grade 2. No diverticulum was seen.

The pancreas was estimated to weigh 80 gm., and appeared normal. Both adrenal glands appeared normal.

The right kidney weighed 106 gm. The capsule stripped with ease revealing a smooth, pink surface. The consistency was normal. Lobulations were increased grade 1. Stellate veins appeared normal. There were numerous, tiny scars or pits over the surface of the right kidney. There were several 0.2 cm. retention cysts present. The cut surface was pink and the markings were distinct. The cortex measured 0.5 cm. and the medulla 1.4 cm. There was hemorrhage into the peripelvic fat. The pelvis, calices and ureter were filled with old hemorrhage, and there was grade 1 dilatation of the pelvis. The pelvis and ureter were not opened at this time.

The left kidney weighed 385 gm., and answered essentially the same description as the right kidney except that there were two 0.2 cm. scars present on the surface and three 0.2 cm. retention cysts. The cortex measured 0.7 cm. and the medulla 2 cm.

The bladder contained 300 c.c. of bloody urine. It was not dilated. The wall appeared normal. The mucous membrane showed multiple, diffuse ecchymoses present. The perivisceral tissues were also infiltrated with a diffuse hemorrhage. The trigone and ureteral orifices appeared normal.

The prostate measured 3 by 2 by 3 cm., and appeared normal. There was a 10 c.c. hydrocele on the right. Testicular stringing appeared normal.

The breasts were of the normal type.

The thyroid gland weighed 31 gm. The consistency was increased grade 2. There was a diffuse hemorrhage into the right lobe of the thyroid.

Aortic sclerosis was graded 1.

The spinal alignment was normal, and there were exostoses present grade 1.

The brain weighed 1575 gm. The external surface of the brain exhibited an occasional small subarachnoid hemorrhage, the largest being in the left temporal lobe. The sectioned surfaces of the brain revealed a hemorrhage into the substance of the pons with destruction of the major portion and also obliteration of the aqueduct of Sylvius. The hemorrhage extended into the third and fourth ventricles, with infarction of the floor of the fourth ventricle. The left internal capsule also exhibited numerous discrete and confluent small hemorrhages with marked softening of this area. The hemorrhage from the third and fourth ventricles extended into the left lateral ventricle for approximately 1 cm. These hemorrhages were composed chiefly of recently clotted blood and fluid blood. The cerebral sclerosis was estimated to be grade 1. The bony structures at the base of the skull were normal. The spinal cord appeared normal.

Bone Marrow: Ribs and sternum showed no fat and a barely evident background of thin fibrous stroma. Cellularity was increased numerically over the normal content. There were many large clusters of stem cells, although two-thirds of the marrow content consisted of normoblasts. Mitotic figures were abundant and there were moderate numbers of myelocytes and granulocytes.

#### SUMMARY

A case of aplastic anemia which may have been due to exposure to products of the sulfite pulp industry is reported. It is believed that the toxic substance may have been a benzene derivative present in the exhaust gases. In view of this, it seems important, in the case of patients connected with the sulfite pulp industry, to be on the alert for such symptoms as progressive weakness, loss of weight, pallor, bleeding from the mucous membranes, petechiae, dermatitis and stomatitis, which may be indicative of such poisoning. Minor complaints of these workers are also deserving of a careful examination. Failure to make an early diagnosis in such cases may prove fatal.

This examination should include a thorough cytological study of the blood. It must be remembered, however, that both the clinical manifestations and the blood changes in benzene poisoning may vary markedly in different individuals, and, as pointed out by Hunter,<sup>3</sup> may be quite different from the aplastic anemia shown by the case here reported.

Periodic examination of those exposed to fumes of high concentration and of those handling paper pulp might well be considered, as a means of investigating the industrial hazard involved, as well as protecting the workers.

#### CONCLUSIONS

The case presented is of interest because the development of aplastic anemia may have been caused by constituents of the exhaust gases of the sulfite pulp industry. Further investigation of the effect of cymene, other related terpene derivatives, and other constituents in the exhaust gases, as well as products from other sources in the sulfite pulp industry, may reveal significant effects on the

hematopoietic system. It is clearly understood by the author that the inadequate data in this paper can at best serve only to point the way; much more extended study is indicated.

The author wishes to thank the Mayo Clinic for the necropsy report and laboratory data from the forty-ninth day (table 1).

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5. GREENBURG, L., MAYERS, M. R., GOLDWATER, L., and SMITH, A. R.: Benzene (benzol) poisoning in the rotogravure printing industry in New York City, *Jr. Indust. Hyg. and Toxicol.*, 1939, xxi, 417.

## EDITORIAL

### *BRIGHTER BLOOD FOR BLUE BABIES*

BRIGHTER blood for blue babies! Yes, and brighter horizons for the anguished parents of these unfortunate youngsters, the majority of whom succumbed from anoxemia or cerebral thrombosis early in childhood after varying periods of chronic invalidism while the medical profession sat helplessly by with nothing to offer along therapeutic lines. Such is the significance of the daring surgical treatment of congenital malformations of the heart in which there is pulmonary stenosis or pulmonary atresia as reported by Blalock and Taussig<sup>1</sup> within the past year.

Prior to November 29, 1944 when the first operation was performed by Blalock on a 15 month old blue baby girl in whom Taussig had established the diagnosis of tetralogy of Fallot with a severe degree of pulmonary stenosis, there had been no satisfactory treatment for pulmonary stenosis or pulmonary atresia. This operation and the studies leading thereto were undertaken with the conviction that, even though the structure of the heart was grossly abnormal, in many instances it might be possible to alter the course of the circulation in such a manner as to lessen the cyanosis and the resultant disability.

It has long been recognized that one of the principal factors in the production of cyanosis in congenital malformations of the heart is the direct shunting of venous blood into the systemic circulation. In their outstanding studies on cyanosis Lundsgaard and Van Slyke<sup>2</sup> showed that there were four important factors in the production of cyanosis: (1) the height of the hemoglobin, (2) the volume of the venous blood shunted into the systemic circulation, (3) the rate of utilization of oxygen by the peripheral tissues, and (4) the extent of aeration of the blood in the lungs. Blalock and Taussig recognized the fact that to induce an increase in the blood flow through the pulmonary circuit should result in an improvement in the oxygenation of the blood with a subsequent decrease in the preëxisting compensatory polycythemia, the cyanosis, and the incapacitating physiological effects of the anoxemia in certain children with congenital heart disease.

The feasibility of anastomosing a systemic artery to one of the pulmonary arteries in experimental animals was demonstrated by Levy and Blalock<sup>3</sup> six years ago. As far as they were aware, this was the first time that both the course and function of a large artery had been altered. Before undertak-

<sup>1</sup> BLALOCK, A., and TAUSSIG, H. B.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 189.

<sup>2</sup> LUNDSGAARD, C., and VAN SLYKE, D. D.: Cyanosis, *Medical Monographs*, vol. 2, 1923, Williams and Wilkins Company, Baltimore.

<sup>3</sup> LEVY, S. E., and BLALOCK, A.: Experimental observations on the effects of connecting by suture the left main pulmonary artery to the systemic circulation, *Jr. Thoracic Surg.*, 1939, viii, 525.

ing operation on patients, Blalock and his associates performed many experiments in an effort to produce pulmonary stenosis in dogs, but this work met with little success. Finally, in an effort to cause a significant decrease in the oxygen saturation of the arterial blood, one or more lobes of the lungs were removed from each side of the dog's chest and the main arteries and veins of these lobes were connected by end-to-end suture creating bilateral pulmonary arteriovenous fistulas. These procedures resulted in some instances in a pronounced reduction in the oxygen saturation of the arterial blood. As the result of an artificial patent ductus arteriosus made in two such experiments, there was a significant increase in the arterial oxygen saturation. Although this experimentally produced condition was quite different from that seen in patients, it was of interest that the establishment of an anastomosis between systemic and pulmonary arteries caused an increase in the oxygen saturation of the arterial blood despite the fact that several lobes of the lungs had been removed.

Since the "blue baby" operation was devised to compensate for inadequate flow of blood to the lungs, it seemed desirable that the anastomosis be made in such a manner that the blood from the systemic artery would be able to reach both lungs. It was obvious that the suture anastomosis could not be made to the main pulmonary artery because occlusion of this vessel for more than a few minutes causes death. Hence, it appeared that the anastomosis should be made just distal to the division of the main pulmonary artery and that the side of the vessel should be used in order that the blood might flow to both lungs. In brief, the operation consists in the creation of an artificial ductus arteriosus by making an end-to-side anastomosis between a branch of the aorta—either the subclavian or innominate artery—and one of the pulmonary arteries. Because of its larger calibre the innominate artery has proved to be the more satisfactory in children with pronounced anoxemia. The anastomosis of the innominate artery to the pulmonary artery diverts a large volume of blood from the systemic circulation into the pulmonary circulation. By this means, the volume of blood which reaches the lungs for aeration is increased. It follows that a greater volume of oxygenated blood is returned by the pulmonary veins to the left auricle and left ventricle, and consequently a greater volume of oxygenated blood is pumped out into the systemic circulation. Thus the operation enables some blood to bypass the obstruction to the pulmonary circulation.

At the time the original report was submitted for publication, three children, each of whom had a severe degree of anoxemia, had been subjected to this operative procedure. Clinical evidence of improvement was striking and included a pronounced decrease in the intensity of the cyanosis, a decrease in dyspnea, and an increase in tolerance to exercise. In the two cases in which laboratory studies were performed, there was a decline in the erythrocyte count, hemoglobin level and the volume of packed red blood cells, an increase in the oxygen content of the arterial blood, a fall in the oxygen capacity, and—most significant—a decided rise in the oxygen saturation of

the arterial blood. In one child the oxygen saturation rose from 35.5 to 79.7 per cent in nine days, and it reached a value of 83.8 per cent 24 days after operation.

Since the original report was submitted for publication, Blalock<sup>4</sup> has performed the operation on over 70 blue babies. The great majority have been remarkably benefited, the mortality rate has been amazingly low considering the delicacy of the procedure and the poor physical condition of most of the patients, and post-operative complications such as cerebral damage from ischemia following ligation of the common carotid artery have been extremely rare. At the present writing, the conclusion is justified that the operation may be regarded as a God-send to the blue baby.

The types of abnormality which Blalock and Taussig believe should be benefited by this operation are the tetralogy of Fallot (pulmonary stenosis or atresia, dextroposition of the aorta, interventricular septal defect, and right ventricular hypertrophy), pulmonary atresia with or without dextroposition of the aorta and with or without defective development of the right ventricle (all infants with this condition, in whom the spontaneous closure of the ductus arteriosus cuts off the circulation to the lungs, die at an early age), a truncus arteriosus with bronchial arteries, and a single ventricle with a rudimentary outlet chamber in which the pulmonary artery is diminutive in size. The operation is indicated only when there is clinical and radiologic evidence of a decrease in the pulmonary blood flow. The two outstanding features, both of which should be present, are (1) roentgenographic evidence that the pulmonary artery is diminutive in size and (2) clinical and roentgenographic evidence of absence of congestion in the lung fields. The operation should be performed on the right or left side, depending on which vessel is to be used and on which side the aorta descends, since it is important to bear in mind that the occurrence of a right aortic arch is by no means rare in congenital malformations of the heart which give rise to persistent cyanosis. The operation should not be performed when studies reveal a prominent pulmonary conus or pulsations at the hili of the lungs. It is not indicated in cases of complete transposition of the great vessels or in the so-called "tetralogy of Fallot of the Eisenmenger type," and probably not in aortic atresia. When one considers the many variations in the anatomy of the heart and great vessels which may be encountered in patients with congenital heart disease, it becomes all the more apparent how essential a pediatric cardiologist such as Taussig, who has devoted so much of her life to the study and recognition of these anomalies, must be both for the selection of candidates for surgical therapy and for the decision as to which side of the thorax should best be explored.

So much then for the new and revolutionary surgical treatment of certain forms of congenital heart disease. It is too early to predict what the late results of this radical form of therapy may be. Will these patients

<sup>4</sup> BLALOCK, A.: Personal communication.

eventually succumb to heart failure, will the incidence of bacterial endocarditis be unusually high, or, from the eugenic angle, will these surgically "rouged" blue babies grow up to procreate more of their kind? These are questions that must be left to the future. The immediate results have been nothing short of brilliant, and the medical profession—not to mention the blue babies—may well bow in admiration to the foresighted surgeon and pediatrician who have collaborated so effectively to alleviate one of the most distressing conditions that may afflict an innocent babe.

W. H. B.

## REVIEWS

*Handbook of Physiology and Biochemistry.* By R. J. S. McDOWALL, M.D., D.Sc., M.R.C.P. 898 Pages; 21 × 15 cm. 1945. The Blakiston Company, Philadelphia. Price, \$6.00.

Originally "Kirke's" and later "Haliburton's." The textbook undoubtedly suffers from the inclusion of too much material about which the author has only limited knowledge. Some of the biochemical presentations are vague and misleading so that even one familiar with the subject has difficulty following the thought.

Other material has not been brought up to date. For example, the classical B oxidation of fatty acids is presented without any indication of the newer concepts of fat oxidation. This tendency is frequently evident. The discussion of the Rh factor is unsatisfactory.

Many will not agree with the sentiments of the author who justifies his choice of material by saying in the preface "—and it will do no harm if the student catches a fleeting glance of things he need not know, for soon he will realize that his knowledge of medicine generally must of necessity be most patchy and superficial."

M. A. A.

## BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*The Tissues of the Body. An Introduction to the Study of Anatomy.* Second Edition. By W. E. LE GROS CLARK, F.R.S. 388 pages; 24.5 × 16.5 cm. 1945. The Oxford University Press, New York City.

*A Future for Preventive Medicine.* By EDWARD J. STIEGLITZ, M.D., F.A.C.P. 77 pages; 22 × 14 cm. 1945. The Commonwealth Fund, New York City. Price, \$1.00.

*The Physician's Business.* Second Edition. By GEORGE D. WOLF, M.D. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. 433 pages; 23.5 × 15.5 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, \$6.00.

*An Introduction to Physical Anthropology.* By M. F. ASHLEY MONTAGU, Associate Professor of Anatomy, Hahnemann Medical College and Hospital, Philadelphia. Visiting Lecturer, Department of Sociology, Harvard University. 325 pages; 21.5 × 14.5 cm. 1945. Charles C. Thomas, Springfield, Illinois. Price, \$4.00.

*Manual of Diagnosis and Management of Peripheral Nerve Injuries.* By ROBERT A. GROFF, M.D., Lt. Col., M.C., A.U.S., and SARA JANE HOUTZ, B.S., First Lieutenant (P.T.), A.U.S. With an Introduction by I. S. RAVDIN, M.D. 188 pages; 23.5 × 16 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, \$8.00.

*Ninth Service Command—Conference on Internal Medicine.* Held at Letterman General Hospital—November 7-8, 1945. 106 pages; 27 × 20.5 cm. 1945.



# COLLEGE NEWS NOTES

## A.C.P. POSTGRADUATE COURSES

### SPRING BULLETIN OF POSTGRADUATE COURSES AUTHORIZED BY THE ADVISORY COMMITTEE ON POSTGRADUATE COURSES, THE COMMITTEE ON EDUCATIONAL POLICY, AND THE BOARD OF REGENTS

As in the past the College will again sponsor a series of intensive, advanced short postgraduate courses which will be held at various medical schools and university teaching hospitals throughout the country, in the spring of 1946 and again in the autumn. These courses have been arranged through the generous coöperation of the directors and the institutions at which the courses will be given.

The courses are organized especially for Fellows and Associates of the College, but where facilities are available, they will be open to non-members with adequate preliminary training, preference to be given to non-members in the following order: (1) candidates for membership; (2) Medical Officers in the Armed Forces; (3) physicians preparing for examinations by their certifying boards; (4) other non-members having adequate background for advanced work. By direction of the Board of Regents registrations from non-members of the College may not be accepted more than three weeks in advance of the opening of any course.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration.

*Fees.* \$20.00 per week to members of the College; \$40.00 per week to non-members; Medical Officers of the Armed Forces of the United States and Canada, free. For purely clinical courses where the instruction must be more personalized and individualized for groups of 12 or less, the fees shall be \$40.00 and \$80.00 to A.C.P. members and non-members, respectively.

Detailed bulletin of courses and registration forms are available through Dr. C. C. Shaw, Educational Director, 4200 Pine St., Philadelphia, 4, Pa.

#### Course No. 1—Clinical Allergy (March 4-9; April 8-13; July 8-13)

Massachusetts General Hospital, Boston, Mass.

FRANCIS M. RACKEMANN, M.D., F.A.C.P., Director

(Registration, 6 men only, each week)

Fee: A.C.P. Members, \$40.00 per week; Non-Members, \$80.00 per week; Medical Officers on Active Duty or Terminal Leave, No Charge.

This is an advanced course in Clinical Allergy which is designed for those men who already have some knowledge of the subject and who wish an opportunity to discuss the new advances and the current problems.

The registrants will see and discuss with Dr. Rackemann and his associates the management of patients in the Clinic and in the wards at the Massachusetts General Hospital. Afternoons will be devoted in rotation to methods and problems in the laboratory, to special reading, and to observations of patients and problems in the private office.

Registration will therefore be limited to six men in March, to another six in April, and to a third group of six only during the proposed week in July.

#### Course No. 2—General Medicine (March 18-23, 1946)

Jefferson Medical College, Philadelphia, Pa.

HOBART A. REIMANN, M.D., F.A.C.P., Director

(Minimal Registration, 75; Maximal Registration, 100)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

An intensive course in General and Internal Medicine will be offered by the faculty of the Jefferson Medical College under the Directorship of the Professor of Medicine, Dr. Hobart A. Reimann.

Recent advances in diagnosis and therapy accruing during the war years will be thoroughly presented in an informal style. The majority of the sessions will be held in the Amphitheatre of the Jefferson Hospital, Philadelphia, where illustrative clinical cases will be presented, films and slides shown and clinical pathological conferences will be held.

Course No. 3—General Medicine (March 25–30, 1946)

University of Texas—School of Medicine, Galveston, Texas

CHARLES T. STONE, M.D., F.A.C.P., Director

(Minimal Registration, 25; Maximal Registration, 50)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

A review course in General Medicine will be offered at the University of Texas School of Medicine in Galveston from March 25 to 30, 1946, under the Directorship of Dr. Charles T. Stone, Professor of Medicine. A detailed outline of the course has not yet been received, but registrants will be provided with excellent and valuable instruction in the practical aspects of general medical practice as well as in diagnosis and therapy of Tropical Diseases in the light of modern advances in this field during the recent global conflict.

Clinics and demonstrations will be held at the John Sealy Hospital and associated institutions in Galveston.

Course No. 4—Internal Medicine (April 1–19, 1946)

Massachusetts General Hospital, Boston, Mass.

JAMES H. MEANS, M.D., F.A.C.P., Director

(Minimal Registration, 60; Maximal Registration, 80)

Fee: A.C.P. Members, \$60.00; Non-Members, \$120.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

A general course in the principles and practice of Internal Medicine will be given at the Massachusetts General Hospital under the directorship of Dr. J. H. Means, who is Jackson Professor of Clinical Medicine at the Harvard Medical School and Chief of Medical Services of the Massachusetts General Hospital.

This proposed course will stress the fundamentals of Internal Medicine.

Various members of the Harvard Medical School faculty, who are serving in other Boston hospitals and institutions, will be invited to participate in the presentations.

Course No. 5—Metabolism and Nutrition (June 3–8, 1946)

Nutrition Clinic, Hillman Hospital, Birmingham, Alabama

TOM D. SPIES, M.D., F.A.C.P., Director

(Minimal Registration, 10; Maximal Registration, 15)

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

An intensive personalized course in Metabolism and Nutrition will be directed by Tom D. Spies at the Nutrition Clinic of the Hillman Hospital in Birmingham, Alabama, for a small group of from 10 to 15 men. The course will be devoted to the

various phases of nutrition and nutritional deficiencies in a practical and stimulating manner, including clinics and ward rounds, field studies, and laboratory demonstrations. Deficiency producing diets and therapeutic diets will be stressed. The principles of nutrition and metabolism will be defined, and the diagnosis and treatment of deficiency states will be presented by means of informal discussions and clinics. Nutrition in relation to dentistry, heart failure, and public health will be presented.

Dr. Tom Spies will be assisted by his associates and colleagues from the Medical College of Alabama and the University of Cincinnati College of Medicine.

Course No. 6—General Medicine (April 22–27, 1946)

Emory University School of Medicine, Atlanta, Georgia

JAMES E. PAULLIN, M.D., F.A.C.P., Director

(Minimal Registration, 15; Maximal Registration, 25)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

Under the directorship of Dr. James E. Paullin, an intensive course covering most of the fields of General Medicine will be presented in Atlanta from April 22 to 27, 1946.

The faculty of Emory University Medical School will serve under the leadership of Dr. Eugene A. Stead, Jr., Professor of Medicine.

Clinical instruction of a high order will be provided at the following hospitals: Piedmont, Grady, Emory University and Georgia Baptist Hospitals.

Atlanta is even more beautiful in the spring.

Course No. 7—Gastro-Enterology (April 29–May 4, 1946)

Graduate Hospital, Philadelphia, Pa.

HENRY L. BOCKUS, M.D., F.A.C.P., Director

(Minimal Registration, 50; Maximal Registration, 100)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

A course in Gastro-enterology has been scheduled in Philadelphia from April 29 to May 4, 1946.

Sessions will be held at the Graduate Hospital of the University of Pennsylvania under the Directorship of Dr. Henry L. Bockus. Previous courses sponsored by this group have provided instruction of a high order in this sub-specialty.

Course No. 8—Cardiology (May 6–11, 1946)

Philadelphia General Hospital and the Woman's Medical College of Pennsylvania, Philadelphia, Pa.

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Director

(Minimal Registration, 75; Maximal Registration, 100)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

A course in Cardiology will be given in Philadelphia, Pa., by a composite faculty, under the Directorship of Dr. William G. Leaman, Jr., who is Professor of Medicine of the Woman's Medical College of Pennsylvania.

Sessions will be held during the day at the Philadelphia General Hospital. In the evening, an interesting and rather unusual program, devoted to the basic sciences and their relation to Cardiology, will be given by the members of the preclinical faculty of the Woman's Medical College. Among members of the faculty who will participate are: James O. Brown, Ph.D., Associate Professor and Acting Head of the Department of Anatomy; Mollie A. Geiss, M.D., Professor of Pathology; Lloyd

D. Seager, M.D., Professor of Pharmacology and Toxicology; Roberta Hafkesbring, Ph.D., Professor of Physiology.

Recent advances in anatomy, physiology, pharmacology, and pathology in their relation to cardiac problems will be presented. This program promises information valuable to the general internist as well as to the cardiologist.

Incidentally, this course directly precedes the Annual Session of the College, to be held in Philadelphia from May 13 to 17, inclusive.

Course No. 9—Chest Diseases (May 6–11, 1946)

University of Michigan, Medical School and Hospital, Ann Arbor, Michigan  
JOHN ALEXANDER, M.D., F.A.C.S., Director

(Minimal Registration, 25; Maximal Registration, 50)

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

This will be an excellent course in Diseases of the Chest, under the Directorship of Dr. John Alexander. The staff of the University of Michigan Medical School and Hospital will participate in the presentations, and it is believed that registrants will find this seminar both highly interesting and instructive.

The treatment of wounds and chest conditions resulting from combat and exposure will be emphasized in the light of newer technic and chemotherapeutics developed during the recent global conflict.

This course will be of extraordinary value to internists and specialists as well as to medical officers and civilian physicians.

Course No. 10—Internal Medicine (June 17–28, 1946)

University of California, Medical School and Medical Center San Francisco, California

STACY R. METTIER, M.D., F.A.C.P., Director

(Minimal Registration, 20; Maximal Registration, 40)

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00; Medical Officers on Active Duty or Terminal Leave, No Charge.

Dr. Stacy R. Mettier, Professor of Medicine and Chairman of the Committee on Postgraduate Instruction of the University of California Medical School, will direct a course in Internal Medicine for the College in San Francisco from June 3 to 14, inclusive.

The University of California offers superior facilities, an outstanding faculty and inspiring surroundings for this course, which will precede the Annual Convention of the American Medical Association in San Francisco.

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A final Bulletin of Spring Courses, containing complete descriptions, outlines of courses, faculty personnel, living accommodations, etc., will be published soon and mailed to all members of the College and to non-members who have requested entry of their names on the mailing list.

Arrangements for living accommodations are being concluded; names of hotels and room rates will be published in the final Bulletin. Because of generally crowded conditions throughout the country, it has become very difficult to obtain reservations for single rooms. Most hotels can provide only double rooms with twin beds, which will necessitate doubling up by our registrants for these courses. Please inform the hotel, where you plan to reside, with whom you are willing to share a room.

Autumn Courses, 1946—A number of varied and interesting courses are being arranged for the autumn. Further announcements concerning the development of our educational program will appear in ensuing issues of the ANNALS OF INTERNAL MEDICINE.

Members who are interested in discussing the educational program of our college are invited to write to, or consult with, the Educational Director, C. C. Shaw, M.D.

### 27TH ANNUAL SESSION OF THE COLLEGE, PHILADELPHIA, PA., MAY 13-17, 1946

The 27th Annual Session of the American College of Physicians will be held in Philadelphia, Pa., from May 13 to May 17, inclusive, 1946. Hotel headquarters will be at the Benjamin Franklin Hotel. The general sessions and the exhibits will be located in the Philadelphia Convention Hall, located at 34th Street below Spruce, opposite the Philadelphia General Hospital.

Registration will begin Monday morning at 9 o'clock in the Convention Hall, and the remainder of that morning is unscheduled to allow registrants a chance to familiarize themselves with the technical exhibits.

The first General Session will be held at 2:00 p.m. on Monday, May 13. A General Session will be held each afternoon, Monday through Friday. On Thursday afternoon at 4 p.m. the Annual Business Meeting of the College will be held, directly after the end of the 4th General Session. All Fellows of the College are urged to be present to hear the annual reports of the Officers, to vote in the election of Officers, Regents, and Governors of the College, and to see the President-Elect, Dr. David P. Barr, of New York, inducted into the office of President of the College.

The retiring President, Dr. Ernest E. Irons, of Chicago, is in charge of the program of General Sessions and of Special Lectures. In addition, he is responsible for the program of the Victory Convocation, which will be held Wednesday evening, May 15, at the Benjamin Franklin Hotel, and will be followed by the President's reception to newly inducted Fellows of the College.

Dr. George Morris Piersol, of Philadelphia, has been appointed General Chairman of the Session, and his duties include appointment of Committees, to make local arrangements for the clinic program, the panel program, and the entertainment features, culminating in the Annual Banquet of the College to be held at the Benjamin Franklin Hotel on Thursday evening, May 16.

Arrangements for the clinical aspects of the Session are now well under way. All the outstanding local hospitals have agreed to contribute to our program. Members of the hospital and teaching staffs will present numerous and varied clinics, including ward walks for limited groups, case presentations, and clinical pathological conferences. The Committee on Clinics and the Hospitals participating are as follows:

Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., Chairman  
 University of Pennsylvania Hospital—Dr. T. Grier Miller, F.A.C.P.  
 Jefferson Hospital—Dr. Hobart A. Reimann, F.A.C.P..  
 Temple University Hospital—Dr. Charles L. Brown, F.A.C.P.  
 Pennsylvania Hospital—Dr. David Cooper, F.A.C.P.  
 Graduate Hospital—Dr. Henry L. Bockus, F.A.C.P.  
 Children's Hospital—Dr. Joseph Stokes  
 Institute of the Pennsylvania Hospital—Dr. Kenneth E. Appel, F.A.C.P.  
 Lankenau Hospital—Dr. Edward L. Bortz, F.A.C.P.  
 Presbyterian Hospital—Dr. Joseph T. Beardwood, Jr., F.A.C.P.  
 Hahnemann Hospital—Dr. G. Harlan Wells, F.A.C.P.  
 Woman's Medical College—Dr. William G. Leaman, Jr., F.A.C.P.  
 Jewish Hospital—Dr. Joseph C. Doane, F.A.C.P.  
 Philadelphia General Hospital—Dr. Truman G. Schnabel, F.A.C.P.  
 U. S. Naval Hospital—Captain Walter H. Schwartz, MC, USN

It will be noted that the morning hours may be devoted either to hospital clinics at the various Philadelphia institutions or to a series of scientific lectures of sufficient length to allow the lecturer to cover thoroughly recent advances in his subject by means of lantern slides, graphic charts, moving picture films, and/or other demonstrations. These morning lectures will be held in the Convention Hall from 9:30 to 11:30, and will be followed by panel discussions of outstanding clinical problems by authorities in the various subjects from 12 noon until 1:15 p.m.

A cafeteria in the Convention Hall will provide luncheon from 1:15 to 2:15 p.m.

The General Sessions will take up the remaining portion of the afternoon schedule.

No scientific sessions will be held in the evening.

On Sunday evening, May 12, the Annual Dinner and combined meeting of the Board of Regents and the Board of Governors will take place in the Benjamin Franklin Hotel. The Entertainment Committee promises a delightful and stimulating evening and opening reception on Monday, May 13, from 8 p.m. to 11 p.m. This will probably be held in the Ball Room of the Benjamin Franklin Hotel.

Tuesday evening, May 14, has no official schedule. The date has purposely been left open to provide an opportunity for private dinners, cocktail parties, and theater groups.

On Wednesday evening, May 15, the great Victory Convocation will be held in the Grand Ball Room of the Benjamin Franklin Hotel, where Fellowships will be conferred on those physicians who have qualified for this honor since the outbreak of the war. This is a very important function of the College, and the ceremony should be not only impressive but epic making in the history of our society. The John Phillips Memorial Medal will be awarded to an outstanding scientist. A full attendance is urged, as our retiring President, Dr. Ernest E. Irons, will address us. All present are invited to the President's reception, with dancing, which immediately follows the Victory Convocation.

The Annual Banquet of the College on Thursday evening, May 16, will complete the list of social functions at this 27th Annual Session. The Committee on Arrangements has promised a gala affair which will contribute to the high order of our program and provide a fitting social finale to your Philadelphia visit.

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#### NEW LIFE MEMBERS

The following Fellows of the College have become Life Members: (Listed in the order of subscription.)

Dr. Albert T. Leatherbarrow, Hampton Station, N.B., Canada  
Dr. William M. LeFevre, Muskegon, Mich.  
Dr. Allen H. Bunce, Atlanta, Ga.  
Dr. George H. Anderson, Spokane, Wash.  
Dr. David B. Flavan, St. Louis, Mo.  
Dr. David W. Kramer, Philadelphia, Pa.  
Dr. Charles T. Stone, Galveston, Tex.  
Comdr. O. V. Calhoun, (MC), USNR, Lincoln, Nebr.  
Dr. Harold W. Gregg, Butte, Mont.  
Dr. William W. Alexander, Florence, Ala.  
Dr. Jacob S. Blumenthal, Minneapolis, Minn.  
Dr. George Tryon Harding, III, Columbus, Ohio.  
Dr. Frank G. LeFor, Yakima, Wash.

## GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

Coy C. Carpenter, F.A.C.P., Winston-Salem, N. C.—1 reprint  
 Henry B. Gwynn, F.A.C.P., Washington, D. C.—1 reprint  
 Paul J. Hanzlik, F.A.C.P., San Francisco, Calif.—4 reprints  
 Samuel I. Kooperstein, F.A.C.P., Jersey City, N. J.—1 reprint  
 Louis S. Lipschutz, F.A.C.P., Eloise, Mich.—1 reprint  
 Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—1 reprint  
 George W. Parson, F.A.C.P., Texarkana, Tex.—2 reprints  
 Michael Peters, (Associate), Fort Benning, Ga.—2 reprints  
 Lawrence E. Putnam, (Associate), Washington, D. C.—1 reprint  
 Michael W. Shutkin, F.A.C.P., Milwaukee, Wis.—1 reprint  
 George E. Baker, F.A.C.P., Casper, Wyoming—4 reprints  
 Robert C. Page, F.A.C.P., White Plains, N. Y.—12 reprints

The College Headquarters acknowledges with thanks the gift of the publisher, Instituto Nacional de Cardiologia, copy No. 74 of "Libro Homenaje al Doctor Ignacio Chavez." This volume is a biographical sketch of the career of Dr. Chavez, who is a distinguished Fellow of the American College of Physicians. The volume has been added to our College library.

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Lt. Col. Henry B. Gwynn, of Washington, D. C. entered active service on May 14, 1942, and was promoted to the rank of Major on May 2, 1943, and to Lieutenant Colonel on January 1, 1946.

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Dr. Manfred Kraemer, F.A.C.P., of Newark, New Jersey, was promoted to the grade of Lieutenant Colonel as of November 17, 1945, and was released to inactive duty (his terminal leave ending January 21, 1946) with this rank, to resume his private practice.

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Surgeon General Kirk of the United States Army, in a Bulletin emanating from the Office of the Surgeon General, Technical Information Division, describes in detail the advantages of Army careers for doctors. An extensive program of graduate medical education and research for Medical Corps officers has been established which will attract the interest of younger internists and those who are seeking qualification by the Specializing Boards. Army fellowships, residencies and special courses are in operation to further this program designed to aid in advancing the personnel of the Medical Department from a professional standpoint.

Under a new law, any doctor, physically and professionally qualified, who has been on active duty in the Army since Pearl Harbor, and who is under forty-five years of age, is eligible for appointment in the Regular Army, unless he has been separated from the service under other than honorable conditions.

His grade will be determined by his age, within limits, or his length of service as a commissioned officer in the Army, whichever is the greater factor. Commissions will encompass the ranks of First Lieutenant, Captain and Major.

The opportunities outlined above are also available to officers in the Pharmacy and the Sanitary Corps and also in the Medical Administrative Corps. Application blanks may be obtained at any Army installation or unit headquarters or upon written request to the Adjutant General's Office, War Department, Washington 25, D. C. Applications must reach the Adjutant General's Office not later than March 10, 1946.

## FELLOWSHIPS IN MEDICAL RESEARCH

The National Research Council is offering fellowships in the fields of cancer research and anesthesiology to veteran medical officers returning to civilian life from the Armed Forces. These fellowships are intended for men, as a rule, under thirty-four years of age, and are scheduled for a period of one year of research. Application forms may be obtained from the Chairman, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

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## REFRESHER TRAINING FOR DOCTORS LEAVING SERVICE

According to News Notes, No. 35, of December 31, from the Technical Information Division, Office of the Surgeon General, refresher training of 12 weeks' duration will be given Army doctors leaving the service who desire to brush up on latest developments in fields of medicine, surgery, or neuropsychiatry in which they may not have been actively practicing during the past year.

This training, which will prepare retiring Army doctors for return to private practice with latest knowledge of medical advances made during the war, will be given at Army hospitals until June 30, 1946. Reserve Corps, National Guard, and AUS Medical Corps officers who are to be separated will be eligible for this schooling.

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Lt. Col. Henry B. Gwynn, MC, AUS, F.A.C.P., has been appointed Director of the Reconditioning Consultants Division, Office of the Surgeon General.

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Thomas Parran, M.D., F.A.C.P., Surgeon General of the U.S. Public Health Service, states that there are 900 vacant full-time positions in state and local health departments. Half of these vacancies are being held for individuals on leave in the military service. The other half are vacancies without restrictions waiting to be filled by qualified physicians.

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Captain Forrest M. Harrison, MC, USN, F.A.C.P., has been appointed Director of the Psychiatric Personnel Placement Service, which is designed to aid physicians and psychiatrists in making contact with training opportunities, such as residencies, postgraduate courses, fellowships, and desirable institutional appointments.

This newly established Psychiatric Personnel Placement Service is sponsored jointly by the American Psychiatric Association and the National Committee for Mental Hygiene.

Inquiries should be addressed to Captain Forrest M. Harrison, MC, USN, National Committee for Mental Hygiene, 1790 Broadway, New York City 19.

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Colonel John R. McBride, MC, AUS, F.A.C.P., has been appointed an Associate in Medicine at the Peter Bent Brigham Hospital to work under the direction of Dr. George W. Thorn, F.A.C.P.

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Lieutenant Colonel Louis S. Lipschutz, MC, AUS, F.A.C.P., has been appointed Medical Director (Psychiatric) of the Wayne County General Hospital, Eloise, Michigan.

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Dr. George X. Schwemlein, F.A.C.P., Co-Director of the Chicago Intensive Treatment Center and Passed Assistant Surgeon (Reserve), United States Public



Health Service, addressed a combined meeting of the Cincinnati Academy of Medicine, Health Department and Dermatological Society on October 16, 1945, on the subject, "The Present Status of Penicillin in the Therapy of Syphilis."

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Colonel William B. Meister, MC, USA, has been appointed Superintendent of the St. Luke's Hospital in Newburgh, New York.

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Dr. Edward L. Bortz, F.A.C.P., of Philadelphia, who was recently discharged from military service with the rank of Captain in the Medical Corps of the U.S. Naval Reserve, discussed "Implications of the Atomic Bomb" before the North Side Branch of the Chicago Medical Society, December 6, 1945, in the Drake Hotel.

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Dr. George W. McCoy, F.A.C.P., Professor and Director of the Department of Public Health, Louisiana State University School of Medicine, New Orleans, has been appointed Acting Dean.

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Dr. Clement C. Fenton, F.A.C.P., Professor and Head of the Department of Pathology of the West Virginia University School of Medicine, Morgantown, West Virginia, has been elected President of the newly organized Association of Pathologists of West Virginia.

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Dr. Theodore G. Klumpp, F.A.C.P., of New York City, is checking on clinical experiments using organic antimony compounds in the treatment of filariasis, at the School of Tropical Medicine, San Juan, Puerto Rico.

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Tulane University School of Medicine, New Orleans, Louisiana, has received a bequest in the amount of \$1,075,000 for endowment of the Chair of Tropical Medicine.

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The New York State Department of Health has available a limited number of Fellowships for veteran medical officers who wish to devote their careers to the practice of civilian public health on a full time basis. Fellowship provisions are generous and include tuition for study at a postgraduate school of public health leading to a master's degree. Additional information and application blanks may be obtained from the New York State Department of Health, Albany 1, New York.

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Colonel Eugene C. Eppinger, MC, AUS, F.A.C.P., has been appointed Assistant Dean in charge of courses for graduates at the Harvard Medical School, Boston. Colonel Eppinger will have charge of the direction of all courses for graduates, including the refresher courses for returning veterans. Initial plans for this postgraduate program have been drawn up by the Committee, under the direction of Dr. Chester M. Jones, F.A.C.P., of Boston.

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Dr. Oscar A. Sander, F.A.C.P., of Milwaukee, Wis., participated in the presentation of a course in Occupational Health and Medicine at the Wayne University School of Occupational Health, which sponsored a twelve week orientation course in this field, beginning January 7.

Dr. Lillian L. Nye, F.A.C.P., formerly of St. Paul, Minn., has been appointed head of the Health Service of the Mississippi State College for Women at Columbus.

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Dr. Felix J. Underwood, F.A.C.P., of Jackson, Miss., who is Executive Officer of the Mississippi State Board of Health, was appointed by Governor Thomas L. Bailey on September 24, 1945, a member of the Mississippi Children's Code Commission.

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Dr. Cornelius P. Rhoads, F.A.C.P., of New York City, delivered the seventh annual Barnard Hospital Lecture before the St. Louis Medical Society on November 20, 1945. Dr. Rhoads discussed the "Nutritional Aspects of the Cancer Problem."

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Dr. S. Douglas Craig, F.A.C.P., Winston-Salem, North Carolina, President of the North Carolina State Board of Health, has been named to direct the Surplus Properties program in that state, serving as the liaison officer between the hospitals and public health agencies in matters affecting surplus Government properties.

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Dr. George R. Minot, F.A.C.P., of Boston, Mass., was honored at a dinner on December 5, 1945, in recognition of his outstanding achievements in medicine and in honor of his sixtieth birthday which he observed December 2. Dr. William B. Castle, F.A.C.P., served as toastmaster, and the speakers included Dr. Henry A. Christian, F.A.C.P., Brookline; Dr. Charles Sidney Burwell, F.A.C.P., Dr. Elliott P. Joslin, F.A.C.P., Dr. James Howard Means, F.A.C.P., and Dr. Francis M. Rackemann, F.A.C.P., all of Boston.

Dr. Reginald Fitz, F.A.C.P., of Boston, representing the President and the House of Delegates of the American Medical Association, presented to Dr. Minot its Distinguished Service Medal for his achievements.

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Dr. Joseph T. Roberts, (Associate), of Washington, D.C., was chosen the Davidson Lecturer of the Medical Society of the District of Columbia in 1945. Dr. Roberts, Adjunct Clinical Professor of Medicine at Georgetown University School of Medicine, submitted a paper on "The Rôle of the Small Vessels and Nerves of the Heart in Heart Failure and Cardiac Pain."

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Dr. William F. O'Donnell, F.A.C.P., of the Georgetown University School of Medicine, Washington, was promoted to the rank of Professor and Acting Director of the Department of Pediatrics.

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Dr. Richard Hugh Wood, F.A.C.P., of Atlanta, Ga., has been appointed Associate Professor of Medicine at Emory University Medical School and Physician-in-Chief at Emory University Hospital.

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Dr. Charles L. Hess, F.A.C.P., of Bay City, Mich., has been reappointed a member of the State Advisory Committee for Vocational Rehabilitation, representing the Michigan State Medical Society.

Dr. Raymond Hussey, F.A.C.P., of Detroit, representing Wayne University, is a member of the Rehabilitation Advisory Committee.

The following Fellows of the American College of Physicians were elected to officership in the Institute of Medicine of Chicago by the Board of Governors on December 12, 1945: Dr. Ernest E. Irons, President of the Institute; Dr. George H. Coleman, Secretary; and Dr. Grant H. Laing, Treasurer. Dr. Italo F. Volini, F.A.C.P., was elected to membership on the Board of Governors for a term of five years.

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Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., who has been Professor of Preventive Medicine and Public Health, Division of Public Health Administration and Epidemiology, University of Minnesota Medical School, has been elected Editor-in-Chief of the *Journal of the American College of Chest Physicians*.

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Dr. Wann Langston, F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine at the University of Oklahoma School of Medicine, Oklahoma City, has been appointed Acting Dean of the school.

Dr. Samuel M. Feinberg, F.A.C.P., of Chicago, and Dr. Robert A. Cooke, F.A.C.P., of New York, presented papers at the seminar of the American Academy of Allergy recently at the New York Postgraduate Medical School.

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A Research Fund sponsored by the American Life Convention and the Life Insurance Association of America for grants to support fundamental research in cardiovascular disease and allied disorders, has been created through the coöperation of one hundred and forty-six life insurance companies in the United States and Canada by establishing the Life Insurance Medical Research Fund.

Dr. Francis G. Blake, F.A.C.P., of New Haven, was named Chairman of the Advisory Council of eight members, among whom are the following Fellows of the American College of Physicians: Dr. Eugene M. Landis, Boston; Dr. Robert F. Loeb, New York; Dr. Seeley G. Mudd, Los Angeles; and Dr. Cecil J. Watson, of Minneapolis; which council will assist the board of directors of this fund in making grants. Application blanks may be obtained from Dr. Blake's office at Yale University School of Medicine, New Haven 11, Conn. Applications must be transmitted in duplicate through the administrative officer of the institution making application.

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Dr. Karl Figley, F.A.C.P., Toledo, Ohio, has been elected a member of the temporary Executive Committee of the International Association of Allergists. Plans are under way to hold the First International Congress in Paris in 1948. The first Pan American Congress of the American College of Allergists is planned for Oakland, Calif., June 28-30.

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The American Gastroenterological Association will hold its annual meeting at the Hotel Claridge, Atlantic City, May 24-25. Dr. Jacob Arnold Bargen, F.A.C.P., Rochester, Minn., is Secretary.

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The Aero Medical Association of the United States will hold its annual convention at the Edgewater Beach Hotel, Chicago, April 7-9.

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The American Public Health Association has announced that it will hold its 74th annual meeting at Cleveland either during the week of November 11 or November 18, 1946. Further announcements will follow.

## SCHEDULE OF ORAL EXAMINATIONS—1946

## AMERICAN BOARD OF INTERNAL MEDICINE

1 West Main Street  
Madison 3, Wisconsin

	Date Oral Exam.	Closing Date for Filing Application	For Candidates Residing in the Following States			
Philadelphia Pa.	May 9-10-11 1946	March 15, 1946	New Hamp. Maine Vermont Mass.	Conn. New York Penna. New Jersey	Maryland Rhode Is. West Va. Virginia No. Carolina	So. Carolina Georgia Florida Dist. of Col. Delaware
San Francisco Calif.	June 27-28-29 1946	April 15, 1946	Montana Idaho	Utah Washington	Oregon Nevada	California Wyoming

The above schedule will be sufficiently flexible to accept eligible candidates who are in the service and have a change of station before the examination.

The Board will appreciate your kind consideration in not requesting admission unless you are reasonably sure of being present. The difficulty of transportation and late trains may interfere with an efficient schedule. It is hoped, however, that all candidates will be able to obtain train and hotel accommodations.

The Board will find it difficult to accept applications after the closing date except for officers who have just returned from overseas and have been unaware of the closing dates.

The Committee on Credentials will meet at the College Headquarters in Philadelphia about the middle of April and again on May 12, 1946. No more meetings of this Committee will be held thereafter until the late autumn of 1946. All proposals for membership and advancement to Fellowship must be filed with the Committee on Credentials thirty days prior to any meeting of this Committee.

Candidates for admission to the College who reside in Eastern Pennsylvania must be endorsed by Dr. Edward L. Bortz, of Philadelphia, who is Governor for this district.

Candidates residing in Michigan must be endorsed by the Governor for Michigan, Dr. Douglas Donald, of Detroit.

Candidates for membership who are practicing in the State of Washington must be endorsed by Dr. Charles E. Watts, of Seattle.

The Board of Regents and the Officers of the College are grateful to Dr. Thomas M. McMillan, Dr. Patrick L. Ledwidge, and Dr. Edwin G. Bannick, who served as Acting Governors of these areas during the leave of absence of the appointed Governors on military duty.

Because of the volume of applications for Clinical Fellowships in Medicine, it was found necessary to establish a closing date for filing applications as of February 1, 1946.

Funds are available for one or two additional Research Fellowships. Applications will be accepted until April 1, 1946. Blank forms may be obtained from the office of the Educational Director, 4200 Pine Street, Philadelphia 4, Pa.

Dr. LeRoy B. Duggan, F.A.C.P., has been retired from active duty in the United States Naval Reserve and is now located in the Medical Arts Building, Houston, Texas. He is Visiting Physician at the Jeff Davis Hospital, Internist at the Hermann Hospital, Consulting Internist at the Southern Pacific Hospital, and Associate Professor of Clinical Medicine at Baylor University College of Medicine.

Dr. Lorenz M. Waller who is on terminal leave from the Medical Corps of the Army has resumed his work as Senior Physician on the Attending Staff of the Los Angeles County Hospital and on the Attending Staff of the Hollywood Presbyterian Hospital. He is on the Associate Staff of the Queen of Angels Hospital also. His office is at 1680 N. Vine Street, Hollywood.

Dr. Joseph B. Cady, following his discharge recently from the Army, is now in charge of the Section of Cardiology and Thoracic Medicine at the Guthrie Clinic of the Robert Packer Hospital, Sayre, Pennsylvania. Before the war Dr. Cady was located in Lebanon, Pennsylvania.

Dr. D. Sergeant Pepper, F.A.C.P., Philadelphia, Pa., following separation from the Medical Corps of the Army as Lieutenant Colonel, has accepted a full time appointment in the medical department of the Provident Mutual Life Insurance Company of Philadelphia.

Dr. James Roby Gudger, F.A.C.P., formerly of West Hartford, Conn., has retired from active duty in the Naval Reserve, and on January 2, 1946, assumed the office of Medical Director of the Mutual Life Insurance Company of New York, with headquarters at 34 Nassau St., New York City.

#### RETIREMENTS FROM MILITARY SERVICE

Since the last publication of this journal the following members of the College have been reported retired or on terminal leave:

Leonard M. Asher, Los Angeles, Calif. (Major, MC, AUS)  
 Noyes L. Avery, Jr., Grand Rapids, Mich. (Major, MC, AUS)  
 John A. Baird, Fargo, N. D. (Major, MC, AUS)  
 Louis J. Benton, Ogdensburg, N. Y. (Capt., MC, AUS)  
 Reuben Berman, Minneapolis, Minn. (Lt. Col., MC, AUS)  
 Maxwell G. Berry, Kansas City, Mo. (Lt. Col., MC, AUS)  
 Philip B. Bleecker, Memphis, Tenn. (Major, MC, AUS)  
 Franklin B. Bogart, Chattanooga, Tenn. (Major, MC, AUS)  
 Clarence H. Boswell, Rockford, Ill. (Lt. Col., MC, AUS)  
 Russell Stanton Bray, Providence, R. I. (Capt., MC, USNR)  
 Joseph B. Cady, Sayre, Pa. (Lt. Col. MC, AUS)  
 Lee D. Cady, St. Louis, Mo. (Col., MC, AUS)  
 John W. G. Caldwell, Des Moines, Iowa (Squadron Leader, RCAF)  
 F. Benjamin Carr, Worcester, Mass. (Capt., MC, USNR)  
 Edward Patterson Childs, New York, N. Y. (Lt. Comdr., MC, USNR)  
 Abraham G. Cohen, New York, N. Y. (Lt. Col., MC, AUS)  
 Leon H. Collins, Jr., Philadelphia, Pa. (Lt. Col., MC, AUS)  
 Charles A. R. Connor, New York, N. Y. (Major, MC, AUS)

Ralph R. Cooper, Detroit, Mich. (Major, MC, AUS)  
J. Antrim Crellin, Philadelphia, Pa. (Comdr., MC, USNR)  
Constance A. D'Alonzo, Wilmington, Del. (Capt., MC, AUS)  
Nicholas John Di Gregorio, Brooklyn, N. Y. (Major, MC, AUS)  
Preston V. Dilts, Pittsfield, Ill. (Lt. Comdr., MC, USNR)  
Robert Deming Donaldson, Kane, Pa. (Comdr., MC, USNR)  
William M. Donovan, Scranton, Pa. (Major, MC, AUS)  
Glenn E. Drewyer, Flint, Mich. (Comdr., MC, USNR)  
Willard G. Drown, Warren, Ohio (Lt. Col., MC, AUS)  
LeRoy B. Duggan, Houston, Tex. (Capt., MC, USNR)  
Garfield G. Duncan, Philadelphia, Pa. (Col., MC, AUS)  
John Keenan Durkin, Philadelphia, Pa. (Capt., MC, USNR)  
John Lewis Dyer, New Orleans, La. (Major, MC, AUS)  
Hamblen C. Eaton, Harrisburg, Pa. (Capt., MC, USNR)  
Kendall A. Elsom, Philadelphia, Pa. (Lt. Col., MC, AUS)  
Harry D. Fein, New York, N. Y. (Capt., MC, AUS)  
Arthur N. Ferguson, Fort Wayne, Ind. (Col., MC, AUS)  
E. Minton Fetter, San Diego, Calif. (Capt., MC, USNR)  
David Finkelstein, Philadelphia, Pa. (Capt., MC, AUS)  
Thomas Fitz-Hugh, Jr., Philadelphia, Pa. (Col., MC, USA)  
Richard D. Friedlander, San Francisco, Calif. (Lt. Col., MC, AUS)  
Mervyn J. Fuendeling, Twin Falls, Idaho (Comdr., MC, USNR)  
Delmar R. Gillespie, St. Paul, Minn. (Major, MC, AUS)  
Henry Spencer Glidden, Andover, Mass. (Comdr., MC, USNR)  
Benjamin E. Goodrich, Pleasant Ridge, Mich. (Capt., MC, USNR)  
Henry B. Gotten, Memphis, Tenn. (Comdr., MC, USNR)  
Stephen A. Graczyk, Buffalo, N. Y. (Major, MC, AUS)  
James R. Gudger, New York, N. Y. (Comdr., MC, USNR)  
William R. Hallaran, Cleveland, Ohio (Lt. Col., MC, AUS)  
Frank W. Halpin, Fort Worth, Tex. (Lt. Col., MC, AUS)  
John Richard Hamilton, Nassawadox, Va. (Comdr., MC, USNR)  
Percy Gatling Hamlin, Santa Barbara, Calif. (Lt. Col., MC, AUS)  
Joseph E. Harenski, Natrona, Pa. (Major, MC, AUS)  
Edward H. Hashinger, Kansas City, Mo. (Col., MC, AUS)  
Arthur O. Hecker, Pittsburgh, Pa. (Lt. Col., MC, AUS)  
Herman S. Hoffman, Washington, D. C. (Capt., MC, USNR)  
Ralph Howard Homan, El Paso, Tex. (Comdr., MC, USNR)  
F. Redding Hood, Oklahoma City, Okla. (Lt. Col., MC, AUS)  
John Davis Hughes, Memphis, Tenn. (Major, MC, AUS)  
J. Warren Hundley, Jr., Philadelphia, Pa. (Lt. Col., MC, AUS)  
Arthur Trimble Hurst, Louisville, Ky. (Comdr., MC, USNR)  
Samuel Hurwitz, Jamestown, N. Y. (Comdr., MC, USNR)  
Milosh Kasich, New York, N. Y. (Lt. Col., MC, AUS)  
T. Douglas Kendrick, Utica, N. Y. (Major, MC, AUS)  
Richard A. Kern, Philadelphia, Pa. (Commodore, MC, USNR)  
Robert W. Kimbro, Cleburne, Tex. (Capt., MC, AUS)  
Robert L. King, Seattle, Wash. (Lt. Col., MC, AUS)  
Melvin Bryon Kirkstein, St. Louis, Mo. (Capt., MC, AUS)  
Leslie R. Kober, Phoenix, Ariz. (Comdr., MC, USNR)  
Arthur M. Kraut, Jersey City, N. J. (Lt. Col., MC, AUS)  
Harold J. Kullman, Detroit, Mich. (Capt., MC, USNR)  
Albert T. Leatherbarrow, Hampton Station, N. B., Canada (Major, MC, RCA)  
Alekssei A. Leonidoff, Poughkeepsie, N. Y. (Lt. Col., MC, AUS)

Ralph U. Leser, Indianapolis, Ind. (Major, MC, AUS)  
Seaborn J. Lewis, Beaumont, Tex. (Capt., MC, USNR)  
McKinley London, Cleveland, Ohio (Comdr., MC, USNR)  
Harold C. Lueth, Evanston, Ill. (Lt. Col., MC, AUS)  
Mischa J. Lustok, Milwaukee, Wis. (Lt. Col., MC, AUS)  
Alexander R. MacLean, Rochester, Minn. (Lt. Comdr., MC, USNR)  
Alexander Marble, Boston, Mass. (Col., MC, AUS)  
Albert G. Markel, Paterson, N. J. (Comdr., MC, USNR)  
Orlando B. Mayer, Columbia, S. C. (Col., MC, AUS)  
Johnson McGuire, Cincinnati, Ohio (Col., MC, AUS)  
H. Easton McMahon, Plandome, N. Y. (Capt., MC, USNR)  
Joseph Medoff, Philadelphia, Pa. (Capt., MC, AUS)  
William B. Meister, Newburgh, N. Y. (Col., MC, USA)  
William C. Meredith, New Rochelle, N. Y. (Lt. Comdr., MC, USNR)  
Louis Merves, Philadelphia, Pa. (Capt., MC, AUS)  
Solomon G. Meyers, Detroit, Mich. (Major, MC, AUS)  
George W. Millett, San Francisco, Calif. (Comdr., MC, USNR)  
John Minor, Washington, D. C. (Col., MC, AUS)  
William J. Mitchell, San Marino, Calif. (Lt. Col., MC, AUS)  
Flavius D. Mohle, Houston, Tex. (Major, MC, AUS)  
Ferrall H. Moore, Redwood City, Calif. (Lt. Comdr., MC, USNR)  
Hugh J. Morgan, Nashville, Tenn. (Brig. Gen., MC, AUS)  
Carlyle Morris, Metuchen, N. J. (Major, MC, AUS)  
John M. Murphy, Detroit, Mich. (Major, MC, AUS)  
Clifford K. Murray, Haverford, Pa. (Lt. Comdr., MC, USNR)  
Walter L. Nalls, Alexandria, Va. (Lt. Col., MC, AUS)  
Louis Ochs, Jr., Shreveport, La. (Lt. Col., MC, AUS)  
Hugh B. O'Neil, Plainview, Tex. (Capt., MC, AUS)  
Robert Clinton Page, White Plains, N. Y. (Major, MC, AUS)  
Oscar A. Palatucci, New York, N. Y. (Lt. Col., MC, AUS)  
Felix Roman Park, Bala-Cynwyd, Pa. (Lt. Col., MC, AUS)  
Victor L. Pellicano, Niagara Falls, N. Y. (Major, MC, AUS)  
D. Sergeant Pepper, Philadelphia, Pa. (Lt. Col., MC, AUS)  
Richard O. Pfaff, San Jose, Calif. (Lt., MC, USNR)  
Francis D. Pierce, Fort Lauderdale, Fla. (Major, MC, AUS)  
Leslie S. Pierce, Greensburg, Pa. (Major, MC, AUS)  
J. William Quinlan, Rochester, N. Y. (Lt. Comdr., MC, USNR)  
Robert B. Radl, Bismarck, N. D. (Lt. Col., MC, AUS)  
Lewis K. Reed, Youngstown, Ohio (Major, MC, AUS)  
Henry A. Rothrock, Bethlehem, Pa. (Capt., MC, USNR)  
Hendrik M. Rozendaal, Schenectady, N. Y. (Lt. Col., MC, AUS)  
Robert B. Rutherford, Peoria, Ill. (Col., MC, AUS)  
Israel A. Schiller, Brooklyn, N. Y. (Major, MC, AUS)  
S. Stanley Schneierson, New York, N. Y. (Lt. Comdr., MC, USNR)  
Carl A. Schuck, Hamilton, Ohio (Col., MC, AUS)  
Norman R. Shulack, New York, N. Y. (Major, MC, AUS)  
George W. Slagle, Battle Creek, Mich. (Comdr., MC, USNR)  
O. Norris Smith, Greensboro, N. C. (Major, MC, AUS)  
H. U. Solovay, Brooklyn, N. Y. (Capt., MC, AUS)  
Carlton R. Souders, Brookline, Mass. (Capt., MC, AUS)  
John Stites, Louisville, Ky. (Major, MC, AUS)  
Emile G. Stoloff, New York, N. Y. (Lt. Col., MC, AUS)  
William G. Talmage, Succasunna, N. J. (Capt., MC, AUS)

Gurney Taylor, New York, N. Y. (Lt. Col., MC, AUS)  
 Harry E. Thompson, Tucson, Ariz. (Capt., MC, AUS)  
 James W. Tice, Hamilton, Ont., Canada (Air Commodore, RCAF)  
 David S. Traub, Louisville, Ky. (Capt., MC, AUS)  
 Woodford B. Troutman, Louisville, Ky. (Lt. Col. MC, AUS)  
 Lorenz M. Waller, Hollywood, Calif. (Col., MC, AUS)  
 W. Kennedy Waller, Baltimore, Md. (Lt. Col., MC, AUS)  
 Charles Edward Watts, Seattle, Wash. (Capt., MC, USNR)  
 Joseph C. Watts, Bayside, Long Island, N. Y. (Major, MC, AUS)  
 Walter David Westinghouse, Buffalo, N. Y. (Lt. Comdr., MC, USNR)  
 Winthrop Wetherbee, Jr., Boston, Mass. (Lt. Col., MC, AUS)  
 T. Preston White, Charlotte, N. C. (Col., MC, AUS)  
 Carl J. W. Wilen, Manhattan, Kan. (Major, MC, AUS)  
 Robert J. Williams, Providence, R. I. (Lt. Comdr., MC, USNR)  
 C. Stuart Wilson, Detroit, Mich. (Major, MC, AUS)  
 George Campbell Wilson, Norwich, Conn. (Comdr., MC, USNR)  
 Henry M. Winans, Dallas, Tex. (Lt. Col., MC, AUS)  
 Walter L. Winkenwerder, Baltimore, Md. (Lt. Col., MC, AUS)  
 Donald E. Wood, Indianapolis, Ind. (Lt. Col., MC, AUS)  
 Francis Clark Wood, Philadelphia, Pa. (Lt. Col., MC, AUS)  
 Raymond J. Wyrens, Omaha, Nebr. (Capt., MC, AUS)  
 Lloyd B. Young, Detroit, Mich. (Lt. Comdr., MC, USNR)  
 William A. Zavod, Mount Vernon, N. Y. (Major, MC, AUS)

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#### DIRECTORY

#### POSTGRADUATE TRAINING FACILITIES

#### INTERNAL MEDICINE AND ALLIED SPECIALTIES

The Office of the Educational Director has compiled the following information from replies received from the various University Medical Schools.

University of Chicago  
 The School of Medicine  
 1945-1946

Opportunities for post-doctorate work exist in many departments of the Medical School, leading to the degree of S.M. or Ph.D.

The Dean of Students is Dr. Lawrence A. Kimpton, Cobb Lecture Hall, Room 203, University of Chicago, Chicago 37.

Columbia University  
 College of Physicians and Surgeons  
 School of Medicine  
 1945-1946

Columbia-Presbyterian Medical Center  
 630 West 168th Street  
 New York 32, N.Y.

Columbia University confers the degree of Doctor of Medical Science on those who complete graduate training over a period of at least three years after the internship in the University or in associated hospitals and laboratories. Only current residents appointed in one of the affiliated hospitals are eligible for registration for the degree.

A wide variety of short courses has been organized in the hospitals and clinics affiliated with the University. These short courses are of two types: Those for the gen-



eral practitioner and those designed to provide advanced instruction, in small groups, to already qualified specialists.

Further information concerning the graduate training (three years) and the short postgraduate courses for practitioners and specialists may be obtained by addressing the Dean of the Faculty of Medicine, Columbia University, 630 West 168th Street, New York 32, N.Y.

Columbia University  
New York Post-Graduate Medical School  
Department of Medicine

The following courses will be given from March through June, 1946:

360—Combined Course in Internal Medicine. Twelve weeks, March 4 through May 24, 1946. Fee for 12 weeks: \$350. Maximum class, thirty. (Enrollment will also be accepted for eleven weeks, March 4 through May 17, fee, \$325; and for ten weeks, March 4 through May 10; fee, \$300.)

This course is designed to meet the needs of returning medical officers for a refresher course covering the major fields of internal medicine, and preference will be given to discharged medical officers in admission to the combined course. Other physicians will be admitted to the following separate courses: Nos. 342, 330, 343, and 337.

Emphasis is placed on therapy, the importance of adequate nutrition, the psychosomatic aspects, and the rôle of geriatrics in each of the diseases under discussion. Diagnostic and therapeutic procedures are demonstrated. Ample time is allotted for the examination of patients in most of the sections.

The following consecutive courses are included in the combined course:

- 342—Normal and Pathological Physiology.  
Ten days; March 4–15, 1946. Fee, \$75.
- 330—Arthritis and Allied Rheumatic Disorders.  
Five days; March 18–22, 1946. Fee, \$45.
- 343—Gastroenterology.  
Ten days; March 25–April 5, 1946. Fee, \$75.
- 337—Diabetes Mellitus, Nephritis and Hypertension.  
Five days; April 8–12, 1946. Fee, \$45.
- 349—Cardiology.  
Four weeks; April 15–May 10, 1946.  
Maximum class, thirty. Fee, \$125.
- 1140—Peripheral Vascular Diseases.  
Five days; May 13–17, 1946.  
Maximum class, twenty-four. Fee, \$45.
- 333—Acute and Chronic Pulmonary Diseases.  
Five days; May 20–24, 1946.  
Maximum class, fifteen. Fee, \$45.

The following additional courses will be given in June, 1946:

- 345—Electrocardiography.  
Five days, June 3–7, 1946. Fee, \$50.
- 348—Parasitology and Tropical Medicine.  
Five days, June 3–7, 1946. Fee, \$45.
- 1100—Symposium on Industrial Medicine.  
Five days, June 10–14, 1946. Fee, \$45.

## 341—Symposium on Internal Medicine.

Ten days, June 17–28, 1946. Registrations will be accepted for the entire ten days or for either the first or second five-day session.  
Fees: \$45 for five days; \$75 for ten days.

*Department of Pediatrics*

## 410—Clinical Pediatrics.

Four weeks, April 1–27, 1946. Fee, \$125.

Detailed programs of these courses will be sent upon request.

Application should be submitted as far in advance as possible, addressed to The Director of the School, 303 East 20th Street, New York 3, N.Y.

Columbia University

New York Post-Graduate Medical School

Second Avenue at 21st Street

New York 3, N.Y.

## Courses in Clinical Medicine, 1945–1946:

## 1100—Symposium on Industrial Medicine.

Five days; March 18–22, 1946.

Minimum class, ten. Fee, \$45.

## 1140—Peripheral Vascular Diseases.

Five days; May 6–10, 1946.

Minimum class, five; maximum, fifteen. Fee, \$45.

## 1143—Physical Therapy.

Five days; April 22–26, 1946.

Minimum class, ten. Fee, \$45.

## 330—Arthritis and Allied Rheumatic Disorders.

Five days; April 1–5, 1946.

Minimum class, five. Fee, \$45.

## 331—Allergy.

Three weeks; April 1–19, 1946.

Minimum class, four; maximum, eight. Fee, \$200.

## 336—Gastroenterology.

Five days; March 4–8, 1946.

Minimum class, five; maximum, fifteen. Fee, \$45.

## 337—Diabetes Mellitus, Nephritis, and Hypertension.

Five days; May 20–24, 1946.

Minimum class, five. Fee, \$45.

## 339—Cardiology.

Five days; May 13–17, 1946.

Minimum class, five; maximum, thirty. Fee, \$45.

## 341—Symposium on Internal Medicine.

Ten days; June 3–14, 1946. Registrations will be accepted for the entire ten days or for either the first or second five-day session.

Minimum class, ten. Fees: \$45 for five days; \$75 for ten days.

## 345—Electrocardiography.

Five days; March 11–15, 1946.

Minimum class, five. Fee, \$50.

## 347—Pathological Physiology: Functional and Chemical Aspects.

Five days; April 8–12, 1946.

Minimum class, five. Fee, \$45.

## 123—Gross and Microscopic Pathology.

2-5 p.m., Monday, Wednesday, and Friday; April 22-May 31, 1946.  
Minimum class, three; maximum, eight. Fee, \$75.

## 415—Symposium on Recent Advances in Pediatrics.

Six days, March 25-30, 1946, and June 17-22, 1946.  
Minimum class, five. Fee, \$50.

Under the direction of Columbia University, postgraduate courses in Clinical Medicine will be given at the Montefiore Hospital, Gun Hill Road (near Jerome Avenue), New York 67; also at the Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29.

The program at the Montefiore Hospital will be devoted to Cardiology and Electrocardiography, and sessions will be held in the afternoons one or two days a week, from March through August.

The program at the Mount Sinai Hospital will include instruction in Allergy, Venereal Diseases, Gastroenterology, Geriatrics; Cardiovascular Diseases, Neurology and Psychiatry, and the Normal and Pathological Physiology of Water and Electrolyte Balance. These courses will be given on a part time basis, one or two days weekly, from February through the middle of June, 1946.

Graduate courses in Neurology and Psychiatry offered by Columbia University College of Physicians and Surgeons and cooperating institutes will be repeated in October, 1946. These courses are designed for a careful clinical survey of Neurology and Psychiatry, with emphasis on the sociological and educational aspects of these subjects. The entire trimester in Neurology and Psychiatry may be taken for a fee of \$250.

Blank form of application for admission may be obtained from Dr. N. D. C. Lewis, Director, Psychiatric Institute, 722 West 168th Street, New York 32, N.Y.

Cornell University Medical College  
1300 York Avenue  
New York City

The Cornell University Medical College at present does not offer work corresponding to that usually described as clinical postgraduate work. Certain professors in the pre-clinical departments offer graduate instruction as an integral part (Group F) of the Graduate School of Cornell University, leading to advanced degrees. The pamphlet entitled "The Announcement of the Graduate School" should be consulted by the candidate before application for admission.

The Creighton University School of Medicine  
Omaha, Nebraska

All departments of the School of Medicine are planning to offer refresher courses for returned veteran medical officers. The Department of Medicine proposes to offer preceptorships in medicine whereby a limited number of students may be assigned to various members in that department. A number of courses of variable length will be given in the following subjects: Cardiovascular Renal Diseases, Gastroenterology, Diabetes, Diseases of the Chest, Endocrinology, General Medicine, Preceptorship, Clinical Pathological Conference, Clinical Basic Science Conference, Bibliography.

Duke University School of Medicine  
Durham, N. C.

See item in this directory listed under "Postwar Planning Committee of the Medical Society of the State of North Carolina."

Harvard Medical School  
Boston, Mass.

The Harvard Medical School offers a six months course in medicine and surgery providing instruction in the fundamental concepts of medical and surgical practice. This course is available to medical officers upon discharge from the Armed Forces. Use will be made of all of the facilities of the Medical School and its affiliated hospitals. This course is not intended to prepare the student for specialization, but is essentially a review course of basic principles.

The course, beginning February 1, accommodates 35 to 40 men, with provision for subsequent enrollment of 5 or 6 veteran medical officers at monthly intervals up to a total of 60 students.

Application for admission should be made to the Assistant Dean of Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston 15, Mass.

Tuition for the course will be \$360.00 plus an additional fee of \$15.00 for medical care and hospitalization. This plan comes under the provisions of Public Law 346, "G.I. Bill of Rights."

University of Illinois  
College of Medicine  
Chicago, Illinois

The University of Illinois College of Medicine, Chicago, offers a variety of opportunities for veteran physicians to continue their professional and scientific education, as follows: (1) a 3 months general clinical course; (2) a number of clinical specialty courses for qualified applicants; (3) residencies in clinical specialties in University hospitals and institutes; and (4) graduate courses in basic medical sciences, leading to the degrees of Master of Science and Doctor of Philosophy.

Fees will average approximately \$100.00 per quarter, and the entire plan will come under the provisions of the G.I. Bill of Rights.

The above opportunities are available as of February 1, 1946.

Further information may be obtained from the Dean, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

Indiana University School of Medicine  
Indianapolis, Indiana

The Indiana University School of Medicine offers four different kinds of postgraduate work for the benefit of returning physicians: (1) a general review of clinical medicine adapted to the needs of the general practitioner; (2) a thorough course of at least 6 months in the basic sciences to prepare candidates for the national board examinations; (3) externe work in the University and City hospitals of 3 to 6 months' duration; and (4) a continuation of the present program of postgraduate training of residents in the various University hospitals and affiliated institutions.

State University of Iowa  
College of Medicine  
Iowa City, Iowa

The College of Medicine of the State University of Iowa presents two types of opportunities to returning veteran medical officers. The first plan consists of an informal course for which no fee will be charged, and which will provide a review and survey of the present trend in medical teaching and practice by attendance at regular undergraduate classes. The second plan consists of a formal refresher course of at least 3 months' duration, which will be available whenever 10 physicians are accepted, and will be repeated as often as the demand exists. This refresher course will fur-

nish a review of the fundamentals of medical practice, particularly in internal medicine, surgery, obstetrics, gynecology, and pediatrics. Continuation studies in the basic sciences will be provided upon request. The fee for the course is \$100. For further information address: The Dean, College of Medicine, Iowa City, Iowa.

University of Kansas  
Kansas City, Kansas.

The University of Kansas has organized a Division of Graduate Medical Education for the purpose of providing postgraduate training to veteran and civilian physicians.

The curriculum is designed to meet as nearly as possible the need for additional training for all groups of physicians. Instruction will be available in the basic sciences, in the specialties of medicine and surgery and ancillary subspecialties.

Intensive review courses from 3 to 10 days in length are planned for the benefit of veterans who desire a quick review before returning to practice. Fees will range from \$10.00 to \$50.00, depending on the length of the course and the nature of the program.

Correspondence should be addressed to the Director, Division of Graduate Medical Education, University of Kansas, School of Medicine, Kansas City, Kansas.

The Long Island College of Medicine  
350 Henry Street, Brooklyn, N.Y.

The Long Island College of Medicine, Brooklyn, New York, has published a spring program of postgraduate courses authorized by their Joint Committee on Postgraduate Education. Most of the courses will run from 8 to 12 or 15 sessions, and are limited in registration to 8 or 10 men. Fees vary from \$20.00 to \$50.00, depending on the length of the course, and presumably can be defrayed through the G.I. Bill of Rights. Special emphasis will be placed on clinical medicine and the allied subspecialties.

Application should be made to the Joint Committee on Post-Graduate Education at the Medical Society Building, 1313 Bedford Avenue, Brooklyn, N.Y.

Mayo Foundation

The Mayo Foundation for Medical Education and Research of the University of Minnesota, Rochester, Minnesota, offers a wide variety of courses in medicine and surgery and hygiene and the various subspecialties.

Detailed information may be obtained from the office of Dr. Donald C. Balfour, Director of the Mayo Foundation.

McGill University Faculty of Medicine  
Montreal, Canada

The Faculty of Medicine of McGill University, Montreal, has set forth an extensive program of graduate instruction dedicated to the needs of medical officers returning to civilian life from the Armed Forces of the Dominion. Refresher courses will be given at McGill University and associated hospitals. In addition, courses in graduate study are available with training towards diplomas in internal medicine in the Clinical Departments of the Faculty of Medicine. Diplomas are also offered in surgery, obstetrics and gynecology, pediatrics, psychiatry, neurology, neurosurgery, ophthalmology, otolaryngology, radiology, and urology. In addition to the above, tutorial classes have been established in preparation for the final examinations of the Royal College of Physicians and for fellowship in the Royal College of Surgeons, Canada.

University of Michigan Medical School  
Ann Arbor, Michigan

The Medical Faculty of the University of Michigan has announced a postwar program of training and review courses for returning medical officers and civilian physicians. The plan essentially provides a graduate program for resident staff appointees, special instructorships, intensive review courses in general medicine, brief review courses in specialized fields, and clinical exercises for practitioners.

Correspondence concerning postgraduate medical instruction and training at the University of Michigan should be addressed to: Dr. Howard H. Cummings, Chairman, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

University of Minnesota Medical School  
Minneapolis, Minnesota

The University of Minnesota Center for Continuation Study announces a series of courses for graduates whose plans for continuation education were interrupted by military service.

These courses have been arranged for veteran medical officers who plan to accept an association with a specialist or obtain a residency or prepare for American Board examinations or return to practice. Continuation courses will be offered in medicine, surgery, and the basic sciences. Classes will be taught at the Center for Continuation Study, Medical School, University of Minnesota Hospitals, Minneapolis General Hospital, Ancker Hospital (St. Paul), and affiliated teaching institutions. Communications should be addressed to Dr. William A. O'Brien, Director of Postgraduate Medical Education.

University of Montreal Faculty of Medicine

The Faculty of Medicine of the University of Montreal is prepared to provide to demobilized medical officers refresher courses of 6 to 8 weeks' duration. A maximum of 15 candidates and a minimum of 10 will be accepted. Specialty courses of 2 weeks will follow refresher courses.

New York Polyclinic  
Medical School and Hospital  
335 to 361 West 50th Street  
New York 19, N. Y.

The New York Polyclinic Medical School and Hospital offers practical instruction in all branches of medicine and surgery. A 6 weeks full time course in medicine provides integrated clinical and didactic study, and covers practical problems in diagnosis and treatment. Ample time is devoted to demonstrations in medical specialties, and opportunity is afforded for the matriculant to supplement this course by an additional 6 weeks of work in the wards and out-patient department of the hospital.

A full time course including the fundamentals of the various medical and surgical specialties, and reviewing established procedures and recent advances in medicine and surgery, is also offered for the benefit of the general practitioner.

For further information, address Edward L. Kellogg, M.D., Medical Executive Officer of the New York Polyclinic.

Postwar Planning Committee of the Medical Society of the State of *North Carolina*

The Postwar Planning Committee of the Medical Society of the State of North Carolina has established review and refresher courses at the University of North Carolina School of Medicine (Chapel Hill), at the Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital (Winston-Salem),

and at the Duke University School of Medicine (Durham). An extensive schedule of ward rounds, clinics, and conferences are available to veteran medical officers who may avail themselves of refresher courses of this nature over a period of three months. A limited number of appointments for a minimum period of nine months will provide training leading to certification in the various specialties. A number of fellowships are available for graduate study, and a certain number of residencies are available in medicine and the allied subspecialties.

Northwestern University  
Medical School  
Chicago, Illinois

The Medical School of Northwestern University has recently organized a program devoted to the satisfaction of the requirements of the American specialty boards for certification. All specialties are included in this program, the fundamental feature of which is the coördination of a group of approximately 150 residencies and fellowships in 10 Chicago hospitals. A Master's degree may be obtained by additional registration in the Graduate School of Northwestern University and the completion of a substantial research project and thesis. Three years is the length of the normal training period; but in the immediate postwar phase, many appointments will be available for shorter periods because of credit for military service allowed by various certifying Boards.

Research assignments are available in all fields of study, but no intensive training of the short review or refresher type is provided. Requests for such training should be referred to the Cook County Graduate School of Medicine, 427 South Honore Street, Chicago—Mr. James Askin, Registrar.

Dr. Arthur R. Colwell is the Director of Medical Specialty Training at Northwestern University, Ward Memorial Building, 303 East Chicago Avenue, Chicago 11.

Ohio State University  
Columbus, Ohio

The College of Medicine of Ohio State University has established a program of postgraduate refresher training, designed especially for returning veterans. Opportunities are available in all departments, and will provide for study and observation of ward patients, review of special procedures and technics, clinical dispensary duty, and full access to both preclinical and clinical facilities and resources of the College of Medicine.

Applications for postgraduate refresher training should be made to Dr. George H. Ruggy, Junior Dean, College of Medicine, Ohio State University, Columbus 10, Ohio.

The University Hospital will adopt a program consisting of a 5-year period of training in residence, which will equip physicians to practice a specialty and qualify them for examination by the national certifying board. Advanced degrees are available to those who satisfy the requirements of the Graduate School, Ohio State University.

Applications should be addressed to Mr. Louis Blair, Superintendent, University Hospital, Ohio State University, Columbus 10, Ohio.

University of Oregon Medical School  
Portland, Oregon

The Medical School of the University of Oregon offers a refresher course for general practitioners; and intensive courses in cardiology, obstetrics, and pediatrics. In addition, specialty refresher courses are offered in various subjects, and a series

of twelve 5-day intensive courses has been established. The program of approved specialty residencies will be continued and, in addition, a veteran residency program has been authorized for veterans only.

Further information concerning reservations, registration, schedules, class quotas, starting dates, etc., may be obtained from the Director of Postgraduate Training, Office of the Dean, University of Oregon Medical School, 3181 S.W. Marquam Hill Road, Portland 1, Oregon.

University of Pennsylvania School of Medicine and  
Graduate School of Medicine  
Philadelphia, Pa.

The School of Medicine will offer a refresher course of 12 weeks' duration to those who wish an intensive comprehensive review in medicine, surgery, and the clinical specialties.

Application for enrollment may be made to Dr. Isaac Starr, Dean, University of Pennsylvania School of Medicine, Philadelphia 4, Pa.

The Graduate School of Medicine specializes in Long-term Graduate Training with basic and advanced instruction leading to clinical specialization. At least one academic year of full time study is required. An additional two years of practical experience under an acceptable preceptor and an original thesis will qualify the student for a M.Sc. (Med.) degree. The fee is \$800.

In addition, the Graduate School of Medicine presents short courses in clinical specialties for students who are already qualified as specialists. These courses vary in length from 2 weeks to 4 months, and the fees will be commensurate with the length of each course.

Information concerning these excellent opportunities for training may be obtained from Dr. Robin C. Buerki, Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

All of the above plans offered by the University of Pennsylvania come under the provisions of the G. I. Bill of Rights.

University of Pittsburgh  
School of Medicine  
Pittsburgh, Pa.

The University of Pittsburgh School of Medicine has organized a refresher course of 8 weeks' duration for the general practitioner, constituting a review of all aspects of clinical medicine. Registration will be limited to a group of 20 to 24 veterans. The fee will be \$150.00, payable under Public Law 346.

Intensive refresher work in a specific subject will not be offered.

Applications should be addressed to the Dean of the School of Medicine, University of Pittsburgh, Pittsburgh 13, Pa.

University of Rochester  
School of Medicine and Dentistry  
Rochester, New York

The University of Rochester School of Medicine and Dentistry provides opportunities for postgraduate training of veteran physicians by means of expansion of their residency program in medicine and surgery and special fields. A 6 weeks' refresher course is designed to present a broad reorientation in the whole field of medicine, and will allow for clinical instruction in the special field of a veteran medical officers' particular interest.



A detailed catalog of facilities in Rochester may be obtained from the Assistant Dean, Dr. George Packer Berry, 260 Crittenden Boulevard, Rochester 7, New York.

Southwestern Medical College  
Dallas, Texas.

The Southwestern Medical College of the Southwestern Medical Foundation located in Dallas, Texas, offers a 2 months' course in medicine and pediatrics for returning medical officers and other interested physicians. Enrollment will be limited to 20 men, and all communications should be addressed to: Dr. Donald Slaughter, Dean of Students, Southwestern Medical College, 2211 Oak Lawn Avenue, Dallas 4, Texas.

Syracuse University  
College of Medicine  
Syracuse, New York

The Syracuse University College of Medicine offers opportunities for study, observation, and clinical experience for returning medical officers and civilian physicians. These exercises will include lectures, clinics, bedside rounds, clinical pathological conferences, and laboratory demonstrations.

Intensive instruction in special fields may be offered to a limited number of physicians.

Address all communications to the Dean, College of Medicine, Syracuse University, 766 Irving Avenue, Syracuse 10, New York.

Temple University School of Medicine  
Philadelphia, Pa.

Temple University School of Medicine will offer a course in Psychosomatic Medicine for the internist and general practitioner from March 4 to March 30, 1946. The fee for the course is \$200. Full details may be obtained by writing to Mrs. Carol Krusen Scholtz, Registrar, 3401 North Broad Street, Philadelphia 40, Pa.

University of Texas  
School of Medicine  
Galveston, Texas

The School of Medicine of the University of Texas presents an extensive postgraduate program in medicine during the current year. Their general policy is to establish individual arrangements which will satisfy individual needs and preferences for each physician who enrolls in their postgraduate training program, which consists of residency training, preclinical courses, externships, and a series of short courses and conferences in general medicine and surgery and the allied specialties.

Communications should be addressed to the Director, Postgraduate Division, The University of Texas School of Medicine, Galveston.

University of Toronto  
Faculty of Medicine

The Faculty of Medicine of the University of Toronto offers a 2 months' refresher course providing instruction in medicine, surgery, obstetrics, gynecology, and pediatrics. This review course for ex-Service medical officers is now under way and will be repeated, beginning April 1, 1946, provided applications are received on or before March 16, 1946.

Tufts Medical School  
Postgraduate Division  
Boston, Massachusetts

The Postgraduate Division of Tufts Medical School in Boston offers a series of postgraduate courses for the general practitioner. Of interest to internists are the following schedules:

Allergy, May 13-17, 1946  
Cardiology, April 29-May 3  
Dermatology, April 1-5  
Electrocardiography, May 13-17  
Endocrinology, May 20-24  
Internal Medicine, May 6-31  
Proctology, April 22-27 and April 29-May 25  
Radiology, April 8-11

Applications for admission should be made to the Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet Street, Boston, Mass.

Tulane University of Louisiana  
School of Medicine  
New Orleans, Louisiana

The Tulane University of Louisiana School of Medicine, Department of Graduate Medicine, presents a schedule for review of general medical practice, as follows:

Diseases of the Cardiovascular System, March 11-16, 1946  
Pulmonary Diseases, March 18-23  
Gastrointestinal Diseases, March 25-30  
Urinary Diseases, April 8-13  
Diseases of Nervous System, April 15-20  
Nutritional and Metabolic Diseases, April 22-27  
Infectious Diseases, April 29-May 4  
Neoplastic Diseases, May 6-11  
Obstetrics and Gynecology, May 13-18  
Traumatology, May 20-25

Tuition fee is \$25.00 per week, and registrants may take as many weeks as desired.

For detailed information write to: Dr. H. W. Kostmayer, Director, Department of Graduate Medicine, 1430 Tulane Avenue, New Orleans 13, La.

Vanderbilt University  
School of Medicine  
Nashville, Tenn.

The School of Medicine of Vanderbilt University, Nashville, Tennessee, offers postgraduate courses in preventive medicine and public health, and also short intensive courses in clinical subjects. Arrangements have been established between Vanderbilt University and the Commonwealth Fund to sponsor fellowships at Nashville in medicine, surgery, pediatrics, obstetrics, and gynecology.

The Registrar of the Medical School will be glad to supply information upon request.

University of Vermont  
College of Medicine  
Burlington, Vermont

The University of Vermont offers a 12 weeks' course in general practice for the benefit of returning veteran medical officers. A 4 weeks' review course in internal medicine and another in surgery are available, in addition to 23 elective subjects which may supplement the daily schedule.

Application for enrollment in these courses may be made through the Office of the Dean, College of Medicine, University of Vermont, Burlington, Vt.

Medical College of Virginia  
Richmond, Virginia

The Medical College of Virginia plans to offer short courses of the refresher type during the current year. Inquiries should be addressed to: Dr. William B. Porter, Physician-in-Chief, Department of Medicine, Hospital Division, Medical College of Virginia, Richmond, Va.

Washington University  
School of Medicine  
St. Louis, Missouri

The Washington University School of Medicine, St. Louis, Mo., has authorized an extensive program of postgraduate courses for medical veterans. The Medical School and affiliated hospitals have made provision for postgraduate instruction in the following categories:

1. Residencies and fellowships in all clinical subjects
2. Fellowships in all preclinical sciences
3. A one-month refresher course in ophthalmology
4. A two-month refresher course in otolaryngology
5. An eight-month graduate course in ophthalmology
6. An eight-month graduate course in otolaryngology

Inquiries may be addressed to the Registrar, Washington University School of Medicine, St. Louis 10, Mo.

George Washington University School of Medicine  
Washington, D.C.

A program for postgraduate instruction offered by the George Washington University School of Medicine for returning medical officers consists of two essential parts. The first is a series of brief review courses covering a number of the specialties of medical practice, beginning February 11 and extending through April 13, 1946. The following subjects will be stressed: Internal medicine, psychiatry and neurology, pediatrics, infectious diseases, obstetrics, general surgery, gynecology, otorhinolaryngology, ophthalmology, anesthesiology, orthopedics, and urology.

This General Review Course is designed primarily for the man who has previously done general practice, or for the younger veteran who wishes a reorientation in all fields before entering upon further specialty training.

The second part of the program consists of a series of preceptorships in the various specialties for the benefit of medical veterans who have previously had specialty training. These preceptorships under certified specialists vary from a few months to several years' association.

A limited number of fellowships in medicine and pediatrics are available at the University Hospital and other affiliated institutions.

The Dean is Dr. Walter A. Bloedorn, 1335 H Street N.W., Washington 5, D.C.

Wayne University  
College of Medicine  
Detroit, Michigan

The Wayne University College of Medicine has organized short postgraduate courses, available for veterans only, in the following subjects: Anatomy, pharmacology, physiological chemistry, dermatology, internal medicine, hematology, psychiatry, ophthalmology, and proctology. These courses are an integral part of the Continuation Curriculum at Wayne University College of Medicine.

Further information may be obtained from the Recorder.

University of Wisconsin  
Medical School  
Madison, Wisconsin

The University of Wisconsin Medical School has established plans for refresher courses and postgraduate training of veteran medical officers. These plans are also available for graduate physicians in civilian practice. The program will consist of four lines of endeavor:

1. A refresher course of 12 weeks' duration for general practitioners.
2. A 2 to 6 months' course for specialists.
3. Residencies of 3 years' duration, leading to specialty certification.
4. Intensive training in the basic sciences for a year or more.

For further information, address: Dean of the Medical School, University of Wisconsin, Madison, Wisconsin.

Woman's Medical College of Pennsylvania  
Philadelphia, Pa.

The Woman's Medical College of Pennsylvania offers postgraduate instruction for medical-officers, veterans and civilian physicians. A general clinical refresher course of 3 months' duration will provide quick review of the principal field of internal medicine. The proposed fee for this course is \$150.00. Registration will be limited to from 8 to 15 graduate students.

A course in cardiology for advanced students will cover cardiac physiology, clinical cardiology, cardiovascular roentgenology, and electrocardiography. Bedside and out-patient instruction will be provided at the Woman's Hospital and affiliated institutions. Registration will range from 5 to 10 students. The course will be 6 weeks in duration; and the fee, \$100.

Further information may be obtained from the Dean of the Woman's Medical College of Pennsylvania, Henry Avenue and Abbottsford Road, Philadelphia 29, Pa.

Canadian veteran medical officers should secure a copy of the booklet entitled "Facts about Your Medical Career on Demobilization," which has been compiled and presented by the Canadian Medical Procurement and Assignment Board, under the authority of the Minister of the Department of Veterans Affairs, and contains general information concerning refresher courses, postgraduate training, placement, and miscellaneous appointments, throughout the Dominion of Canada. This is published by King's Printer, Ottawa, and contains much information of vital interest.

## MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA., NOVEMBER 18, 1945

The regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, November 18, 1945, with President Ernest E. Irons presiding, Mr. E. R. Loveland acting as Secretary, and the following in attendance:

Ernest E. Irons.....	<i>President</i>
David P. Barr.....	<i>President-Elect</i>
Walter W. Palmer.....	<i>First Vice President</i>
James J. Waring.....	<i>Second Vice President</i>
William D. Stroud.....	<i>Treasurer</i>
George Morris Piersol.....	<i>Secretary-General</i>
Jonathan C. Meakins.....	
Charles F. Tenney.....	
Francis G. Blake.....	
Roger I. Lee.....	
Charles T. Stone.....	
Walter B. Martin.....	
William S. Middleton.....	
James E. Paullin.....	
LeRoy H. Sloan.....	
Paul W. Clough.....	<i>Acting Editor, ANNALS OF INTERNAL MEDICINE</i>
Edward L. Bortz.....	<i>Chairman, Advisory Committee on Postgraduate Courses</i>
C. C. Shaw.....	<i>Educational Director</i>

The Executive Secretary read abstracted Minutes of the preceding meeting of the Board, which were approved as read.

The President declared a quorum and requested the Secretary to present communications.

The Secretary read letters from members of the Board who could not be present, chiefly because of transportation difficulties.

PRESIDENT IRONS: Under communications also is a report concerning the discontinuance of the War-Time Graduate Medical Meetings. This was foreshadowed in our meeting last June, and during the interim the American College of Surgeons announced their intention to discontinue this program following the end of the War. I consulted the Executive Committee, and it was its unanimous opinion that the War-Time Graduate Medical Meetings should be concluded, particularly in view of the fact that most Medical Officers now in the Army are thinking more of getting back to their civilian work than they are in advancing their experience in the Service. The American Medical Association, the third participant in this program, likewise, has concurred in its discontinuance. Therefore, it is generally agreed that this program will stop with the current month, or by the first of January, 1946. Again, I think we should express our great appreciation of the efforts of Dr. Edward L. Bortz, and later of Dr. Francis F. Borzell, who, along with representatives of the College of Surgeons and the American Medical Association, have done such a magnificent job. The Chair will entertain a motion to approve the action of the Executive Committee in terminating War-Time Graduate Medical Meetings, and expressing to the members of the sub-committee, as well as to our representatives, our appreciation of their efforts.

. . . On motion by Dr. Jonathan C. Meakins, regularly seconded, a resolution as proposed was unanimously adopted. . . .

PRESIDENT IRONS: Another communication came from the National Academy of Sciences, requesting that the College take a position with respect to the maintenance

of standards by the U. S. Civil Service Commission in the filling of positions of various types, having to do with scientific work. It seemed to your Chairman that the College could speak only for those questions concerning medicine. We were asked to be a little broader in our statement, but it seemed wiser to confine our remarks to those subjects closely allied with medicine, and so a letter was formulated to the National Academy, to the Chairman of the National Research Council, stating that the College feels that standards already established in medicine should be maintained, and for technicians in fields ancillary to medicine standards had already been set up by the Council on Medical Education and Hospitals of the American Medical Association and these should be maintained, and, further, that the College feels that it is not in a position to comment on standards in other professions. The reply was approved by the Executive Committee and dispatched.

MR. LOVELAND: I have a communication and check from Dr. Willard O. Thompson, Chicago, depositing in the Postgraduate Fund of the College a balance of \$713.30 from a course conducted for the College a year ago by Dr. Thompson, representing an unused balance, suggesting it be accepted for use in connection with any postgraduate activities of the College in the Chicago area.

. . . On motion by Dr. Roger I. Lee, regularly seconded and unanimously carried, this contribution was acknowledged with deep appreciation. . . .

MR. LOVELAND: Also in the form of a communication, I have to record that Dr. Louis E. Viko, College Governor for Utah, at the request of President Irons; was the official representative of this College on the occasion of the inauguration of the new President of Utah State Agricultural College.

PRESIDENT IRONS: We will now ask for the report of the Executive Secretary.

MR. LOVELAND: Your Executive Secretary thinks it appropriate to make a brief summary report on his activities through the past year. You will learn more of the details, which will be embodied in Committee reports later.

*Membership:* There has been some gradual falling off in the number of candidates for Associateship and Fellowship during the War, yet that does not necessarily mean there is less membership activity; because of the large number of Associates on military duty who could not present their credentials for Fellowship, there has been a material increase in the amount of correspondence necessary, and we have at all times extended such advice and assistance to these members as has been possible. There is a noticeable increase in the number of inquiries received concerning membership, and we predict from this point forward there will be a marked increase in the number of candidates. The College influence during the War has spread beyond the confines of our own country. Fellows of the College in the Armed Forces have carried the reputation and name of the College to many lands. Witness a letter we received from a physician in Australia, who is a Fellow of the Royal College of Physicians and a Fellow of the Royal Australasian College of Physicians, who said that he had been greatly impressed by his contacts with several of our Fellows in his country, especially because of their great loyalty to the College and their reports on the sterling worth of our organization. He asked that he might too be considered for membership in our College, because he would esteem it not only an honor, but a great privilege to be associated with this organization. We have also received several letters from our members who have shown genuine appreciation of what the College has done during the War, and of our continuing interest in them.

I would remind you that we have a tedious and rather big task in establishing individual records for every Associate who is on military service, in order that we may determine exactly the additional time he has available to qualify for Fellowship. A part of this effort must also be directed toward getting each Associate back into active status and determining the date when he resumes payment of dues.

*Membership Roster and Directory:* In the early part of the summer we launched upon the project of preparing a new Membership Roster. A considerable amount of

work had already been concluded before D-Day, but with the coming of VJ-Day, the impracticability of completing the Roster was wholly apparent. Our more than 1,900 members in Service were shifted in all directions, some started being separated from the Service, our address lists were greatly affected and the work we had already concluded would have had to be revised. It appeared more practical to us to abandon the whole project for the current year and wait until 1946. We shall want advice from the Regents as to whether they would wish us to undertake the publication of a complete Directory in 1946—a Directory that shall include all the customary information published about each member before the War in our regular editions. To our knowledge, 1,927 of our members served in the Armed Forces; already about 225, or about 12%, have been retired. We have no information on which to base our estimates of how many members will still be in the Service by July 1, 1946, but it is to be presumed that the majority of the Reserve Medical Officers may then be retired.

*Annals of Internal Medicine:* Following the onset of the War and the waiver of fees and dues to members, we were faced with a considerable diminution in income. At that time we expressed to you our intention to concentrate on increasing the income which we might obtain from other sources, especially from our journal. We are gratified that we were able to increase the circulation of the journal by more than 42%, and the income from advertising 52%.

*Postgraduate Courses:* In spite of the fact that the Chairman of the Committee on Postgraduate Courses has not been available, due to service in the Pacific, we have nevertheless extended the number of our courses and greatly increased the number of registrations. This feature of the College activity has become so popular, especially with the returning veterans, that for the period these courses are being conducted, a tremendous amount of time is required on the part of the College Staff.

*Regional Meetings:* Our Regional Meeting program, as you know, has been greatly extended until the current year, when the meetings had to be curtailed due to War restrictions. Nevertheless, a later report from one of the Committees will show that we have been active, nevertheless, and are again resuming several of these meetings. It is our prediction that many of the Governors, and a whole host of our Fellows and Associates will wish to have these Regional Meetings continued on the multi-State basis, even after the resumption of our Annual Sessions. These meetings have been inspiring, filled with good fellowship, and have kept the contacts of the College with its members alive and flourishing.

*Educational Director:* By direction of the Board of Regents, at its June meeting, the President, the Secretary-General, and the Executive Secretary were instructed to locate and appoint an Educational Director. Several candidates were interviewed and several more were contacted by mail. The Secretary-General, Dr. Piersol, and I interviewed, among others, Dr. C. C. Shaw, and after telephone consultation with President Irons, his appointment was made on November 1, 1945. During the interim, we have succeeded in obtaining for him a competent secretary, and he is busily engaged in organizing his work. From the beginning, he will take over as his responsibility, under such assistance and advice as we can offer, the planning of the Postgraduate Course program, the post-war returning veterans program and the handling of applications for Research and Clinical Fellowships.

*College Headquarters:* The physical aspects of the College Headquarters building and grounds have been maintained in good condition, but the time will soon come when some replacements will be necessary, both in office equipment and furnishings—in the latter case, especially some of the rugs. The adjoining property, to the south of the Headquarters, also has been maintained in good condition, and is profitably rented. We have not given up the hope that some time in the future we may interest some other medical groups in the adjoining property as their headquarters.

*Office Personnel:* Our greatest difficulty and burden during the past year has actually been that of obtaining and retaining competent office personnel. Several em-

ployees have been replaced several times during the War. More lucrative positions have been available in War industry and we have not escaped from the labor unrest current throughout the country. The work of the College must go on, and in the emergencies that have arisen through stenographers and secretaries leaving, we have had to compete with industry in obtaining competent replacements. The result is that it is now costing the College much more for office salaries than before the War. With the expanding activities of the College and the absolute necessity to do our work promptly and well, it must be anticipated that the cost of office service will be higher than heretofore. As yet in this area, there is little evidence of any change occasioned by the termination of War contracts, etc. In fact, in most of the cities over the country, the situation appears to be growing more stringent, not only in available labor, but in housing conditions. Many of our returning members cannot locate office space in which to resume the practice of medicine.

Our best services are pledged to the College!

*President Irons:* I would like to make reference to the accomplishments of one of the members of our Board. This is without intent to fail to recognize the tremendous services of other members. Dr. William S. Middleton has done an exceedingly good job in England, and the standing of the College there has been greatly enhanced thereby. I cannot help from remarking on the tremendous help that he was not only to the College, but in maintaining the interests of the Medical Officers, particularly in reference to their certification in the American Board of Internal Medicine. We will now have the report of the Secretary-General, Dr. George Morris Piersol.

The Secretary-General, Dr. Piersol, reported the deaths of 25 Fellows and 4 Associates since the last meeting of the Board, as follows:

#### *Fellows*

Baumgarten, Walter	St. Louis, Mo.	August 23, 1945
Brady, Jules M.	St. Louis, Mo.	September 6, 1945
Breisacher, Leo	Detroit, Mich.	April 29, 1945
Breuer, Miles John	Los Angeles, Calif.	October 14, 1945
Burnett, Thomas Ward	M.C., U. S. Army	October 19, 1945
Comroe, Bernard Isaac	Philadelphia, Pa.	September 14, 1945
Ferguson, Donald Renwick	Philadelphia, Pa.	August 27, 1945
Frost, Kendal	Los Angeles, Calif.	September 28, 1945
Groat, William A.	Syracuse, N. Y.	September 9, 1945
Harrop, George A.	Princeton, N. J.	August 4, 1945
Harvey, John Goold	Detroit, Mich.	May 24, 1945
Hecker, Friedrich A.	Ottumwa, Iowa	June 3, 1945
Jones, Clement R.	Pittsburgh, Pa.	September 3, 1945
McFarland, Joseph	Philadelphia, Pa.	September 22, 1945
Miner, Frederick B.	Flint, Mich.	April 26, 1945
Richardson, W. W.	Mercer, Pa.	June 10, 1945
Sawyer, John P.	Cleveland Heights, Ohio	June 17, 1945
Shepard, Benjamin A.	Kalamazoo, Mich.	June 16, 1945
Smith, William H.	Goldsboro, N. C.	September 29, 1945
Stewart, Alexander Hamilton	Harrisburg, Pa.	July 31, 1945
Streker, William S.	Providence, R. I.	July 8, 1945
Tucker, Beverley R.	Richmond, Va.	June 19, 1945
Watson, William V.	Toronto, Ont., Canada	October 20, 1945
Welch, Paul Brown	Coral Gables, Fla.	May 6, 1945
White, Arthur W.	Oklahoma City, Okla.	June 11, 1945



*Associates*

Downs, Charles McCabe	M.C., U. S. Army	June 1, 1945
Inman, Jesse Headen	Bakersfield, Calif.	July 15, 1945
Luft, Raymond	Norwood, R. I.	June 23, 1945
Shoup, Jesse	Washington, D. C.	July 21, 1945

. . . At the suggestion of President Irons, the Board stood in memory of those deceased, and particularly in respect to Dr. Clement R. Jones, who for many years was Treasurer of the College. . . .

Dr. Piersol then reported the following list of 13 additional Life Members since the last meeting of the Board, making a grand total of 400, of whom 34 are now deceased, leaving a balance of 366 (named in the order of subscription):

Sydney E. Johnson	Louisville, Ky.
Fred M. F. Meixner	Peoria, Ill.
Hugo O. Altnow	Minneapolis, Minn.
Harold C. Ochsner	Indianapolis, Ind.
Harry Plummer Ross	Richmond, Ind.
Merton M. Minter	San Antonio, Tex.
Samuel L. Crow	Asheville, N. C.
James F. Anderson	Los Angeles, Calif.
Alexander S. Wiener	Brooklyn, N. Y.
Theodore L. Squier	Milwaukee, Wis.
Frank W. Otto	Los Angeles, Calif.
J. M. Nielsen	Los Angeles, Calif.
Ernest D. Hitchcock	Great Falls, Mont.

. . . On motion by Dr. James E. Paullin, regularly seconded and carried, the report of the Secretary-General was adopted. . . .

PRESIDENT IRONS: Under new business and reports, we shall first have a report from the Committee on Credentials, Dr. George Morris Piersol, Chairman.

DR. PIERSOL: The Committee on Credentials held its regular meeting yesterday. There were 120 candidates for Fellowship under consideration, disposed of as follows:

Recommended for Advancement to Fellowship .....	72
Recommended for Election to Direct Fellowship .....	9
Recommended for Election First to Associateship .....	5
Deferred .....	22
Rejected .....	12
	<hr/>
	120
	<hr/>

. . . On motion by Dr. Piersol, on behalf of the Credentials Committee, regularly seconded and unanimously adopted, the following 81 candidates were elected to Fellowship: (*List published in December, 1945, issue*).

DR. PIERSOL (continuing): 145 candidates were considered for Associateship, and disposed of as follows:

Recommended for Election to Associateship .....	94
Deferred .....	31
Rejected .....	20
	<hr/>
	145
	<hr/>

In addition to the above, 5 candidates for direct Fellowship were likewise recommended for election first to Associateship, making a total of 99 on the recommended list.

... On motion by Dr. Piersol, on behalf of the Credentials Committee, regularly seconded and unanimously adopted, the following 99 candidates were elected to Associateship: (*List published in December, 1945, issue*).

DR. PIER SOL (Continuing): The following is a report on the candidates elected to Associateship five years ago, December 15, 1940:

Advanced to Fellowship .....	76
Resigned .....	1
Time Extended because of Military Service .....	39
Dropped for Failure to Qualify .....	28
	<hr/>
	144
	<hr/>

Those who have failed to qualify for advancement to Fellowship, must now be dropped, in accordance with provisions of the By-Laws.

At the last meeting of the Board of Regents the Committee on Credentials recommended the clarification of qualifications for membership in the College and the raising of standards. A motion was proposed requiring that certification by the American Board of Internal Medicine be a prerequisite for Associateship. This aroused much discussion. The matter was not acted upon, but very wisely deferred until this meeting of the Board. The proposal has been more thoroughly explored during the interval, and Dr. Chauncey W. Dowden, Chairman of the Board of Governors, has conferred with that Board, and has analyzed and briefed their replies, and the abstract thereof is available here for any who may be interested. It constitutes a large document, and I shall not take time to read it. It is apparent, with very few exceptions, that the Board of Governors is opposed to this change in the requirements. The Committee on Credentials, individually and collectively, took occasion to discuss this matter with various members of the College and of the Board of Regents. It is now apparent that the proposed change has disadvantages which would seem to offset its advantages. In the first place, it would considerably increase the age at which men would be able to enter the College; in the second place, it would eliminate the five-year period, which is now a definite inspirational term, and these young men would have removed from them the stimulus that heretofore has existed. Furthermore, the Credentials Committee would experience greater difficulties in setting up certain standards for Fellowship. Still further, if no limitation were to be placed on the term of Associateship, because the new proposal provided that an Associate could remain in that status as long as he chose, a situation would be created in which the dominant group in the College would be Associates; the minority would be Fellows; therefrom, a considerable amount of controversy and even factional strife might possibly arise. More important, perhaps, than any of the other considerations, is the fact that had the proposal been adopted, the College might readily be saddled with a large group of Associates for life. No matter how careful the Committee on Credentials might be, there would be no assurance that some of the young men elected to Associateship might in time be found to be undesirable members later on, and there would be no remedy, whereas at the present time an Associate must qualify for Fellowship within a maximum term of five years, or be discontinued on the Roster.

The Credentials Committee, after considering these objections, is not now inclined to press the matter of adoption of the previous recommendations. It does, however, feel convinced that the present regulations and rules that have been drawn up are totally inadequate. We must set up other more clear-cut and satisfactory criteria

upon which to base the election of Associates. The Committee is confronted with its most difficult task in the election of Associates. It is much better not to elect a man as an Associate than, having taken him in, to terminate his membership.

The Committee, therefore, proposes a motion that the Chair appoint a Committee of five, composed of two members from the Board of Regents, preferably not members of the Committee on Credentials, two members of the Credentials Committee and one from the Board of Governors, to explore the whole situation with regard to admission requirements, and to bring in at the next meeting of this Board definite, carefully considered recommendations.

... The motion was seconded by Dr. James E. Paullin, and, after general discussion, was unanimously adopted. ...

President Irons appointed the following Committee:

From the Board of Regents:	Dr. William S. Middleton, Chairman
	Dr. James E. Paullin
From the Credentials Committee:	Dr. George Morris Piersol
	Dr. Wallace M. Yater
From the Board of Governors:	Dr. George H. Lathrope

... On motion by Dr. James E. Paullin, seconded and regularly carried, the report of the Committee on Credentials was adopted as a whole. ...

PRESIDENT IRONS: Next is the report of the Committee on Public Relations, Dr. Roger I. Lee, Chairman.

DR. LEE: The meeting of the Committee on Public Relations was held November 17, with Dr. Ernest E. Irons and Dr. Lee present, and with the benefit of Dr. James J. Waring and Dr. Francis G. Blake sitting in. The Committee had a communication from the National Advisory Health Council and the National Advisory Council, regarding the National Research Foundation, which is the so-called Bush Report with the corresponding legislation. This was a report broadcast to all medical bodies. The Committee discussed in full various aspects of the present legislation, proposed legislation in regard to the so-called National Research Foundation. The Committee recognized at once that the old situation is in a state of flux and change. The Committee also recognized that the American College of Physicians, together with the American College of Surgeons and the American Medical Association, participates in a joint Committee on Post-War Medical Service, and that this Committee has a sub-committee on the very subject and has made an extensive report under the Chairmanship of Dr. Francis G. Blake.

The Committee endorses the general principles of the so-called Bush Report with particular reference to freedom of research. The Committee endorses the report of the sub-committee of the Joint Committee on Post-War Medical Service, and requests that this report be circularized to the Board of Regents and the Board of Governors; furthermore, that this report, with the endorsement of the Regents of the American College of Physicians, be sent to Senators Kilgore, Magnuson, and other individuals, also to the Joint Committee on Post-War Medical Service, and published in the "Annals." This matter is of very great importance to all members of the medical profession and of the College, and various changes from time to time will be suggested in these Bills. A general report of endorsement seems to the Committee to be much preferable to anything that is more specific. The Committee has a very acute appreciation of the fact that a good many physicians, a good many members of the College, Regents and Governors, have no real first-hand knowledge of this important subject, and it feels by circularizing in this fashion and publication of this report in the "Annals" that information may be spread. I move the adoption of this portion of the report.

... The motion was seconded and opened for discussion. ...

DR. WALTER W. PALMER: I am delighted with the recommendations of the Committee on Public Relations. A large number of the two Committees, one of which is headed by me, met in Baltimore last Wednesday, with the view of organizing for political purposes; that is, to get some money to work. There are two Bills really important, the Kilgore and the Magnuson Bills. Medicine is concerned with what Kilgore may be standing out for, a political appointment of a director, and an Advisory Committee which will have on it representatives from the Services. We feel liaison relationship between a committee of that sort is far preferable. The Kilgore group is changing its Bill almost daily; it is difficult to know where they stand; so our two Committees last Wednesday agreed to stick to principles and not compromise, to organize a committee with a chairman, Homer Smith, and we may want to get your help in writing to Senators and Representatives later on.

DR. FRANCIS G. BLAKE: I am very pleased with the action of the Committee. However, action of this kind without compromise backs the Bush Report point of view, with particular reference to the necessity for freedom of research, if a National Research Foundation is to be established, and should be of value; at least in changing the points of view in Congress, where a National Research Foundation is looked upon merely as a means of coordinating research by federal bureaus. That does not meet the problem at all.

DR. JAMES J. WARING: I too am most gratified that this action has been recommended by the Committee on Public Relations. All the members of the College ought to be deeply concerned and ought to be thoroughly informed about this matter, and ought to make their opinions known in Washington, not only by a resolution of this nature, but by letters addressed to their Representatives.

... The motion was unanimously adopted. ...

DR. LEE (Continuing): The Committee reviewed the cases of one Fellow and one Associate who are disabled and out of practice, and provided for the waiver of their dues for 1945 and until their recovery and resumption of work in the future. The Committee also reviewed the resignation of one Fellow and recommended that inasmuch as his resignation was caused by a disabling illness, that he be retained on the Roster and his dues waived for 1945 and until his recovery and resumption of practice.

... On motion by Dr. Lee, seconded and regularly carried, the recommendations concerning the fees and dues cases and the case of resignation were approved and the Committee's report was accepted as a whole. ...

PRESIDENT IRONS: Next will be the report of the Committee on the Annals of Internal Medicine, Dr. Walter W. Palmer, Chairman.

DR. PALMER: The Chairman met with Dr. Clough and Dr. Irons at the College Headquarters on November 17, at 4:00 p.m. Drs. Fitz and Waring could not be present. The Executive Secretary had prepared a cost analysis, which is submitted:

*Comparative analysis for the past six Volumes, ending June 30, 1945*

With regard to volume, circulation and costs, it is to be noted that there has been a slight decrease, because of the War, in the amount of scientific matter, an increase in the amount of news notes, a very marked increase in the amount of paid advertising, and a marked increase in circulation. As a matter of fact, the circulation at the present time exceeds 7,500 copies per month, but it is anticipated that due to Army cancellations, there will be a decrease of perhaps a thousand copies per month in the course of the next year. Particularly should be noted the marked increase in the surplus from operations. This surplus has been extremely valuable in carrying on the work of the College during the period when our other income was greatly reduced, because of the absence of annual exhibits and the waiver of dues

of members on military duty. It is not reasonable to expect the surplus to be as great for the coming year as in the past year, because it is certain that many of the military orders will be eventually cancelled. As a matter of fact, cancellations are starting now to come in.

The desirability of seeking more book reviews was discussed. It was suggested that the Editor make a list of suitable reviewers in the several fields of medicine, solicit coöperation and refer worth while books for reviews from them to him.

During the past year the Committee has approved the expenditure of \$800.00 to cover the cost of colored plates in publishing an excellent article on hepatitis by Dr. C. J. Watson, of Minneapolis.

The group considered the request of Hubert Winston Smith to publish in the ANNALS a series of articles on medico-legal topics. Such a series, under his supervision, was published three years ago. It was decided to refer the matter for an expression of opinion from the Board of Regents before making final recommendations to the Editor.

Again the Committee wishes to express its appreciation to the Editor and to the Executive Secretary for the success of the ANNALS OF INTERNAL MEDICINE.

The Committee would particularly like to have the Regents express their opinion for or against another issue of the ANNALS devoted to medico-legal medicine under Dr. Smith's supervision.

... There was general discussion, for the benefit of the Editor's direction, among various members of the Board, including Doctors Piersol, Lee, Palmer and Mr. Loveland, and the general reaction to publish another issue on this subject was unfavorable. ...

... On motion by Dr. David P. Barr, seconded by Dr. James E. Paullin, the report was adopted. ...

PRESIDENT IRONS: Next is the Acting Editor's report, Dr. Paul W. Clough.

DR. CLOUGH: The ANNALS has been published about as usual. There is just as much difficulty in the printing establishment in getting the journal out promptly. So far as material is concerned, it is coming in a little better and the quality of material is also better. We have enough material on hand to carry through March or April, as far as main articles are concerned. We will still welcome any good articles from members of the Board of Regents, or from others. It is possible now to resume the use of better paper and to make our journal more presentable. Dr. Pincoffs, the Editor, is recuperating from a major operation at the Walter Reed General Hospital, and although he is now at home, he is not well enough to take up any business topics. However, as far as I am aware, he expects to resume his work as Editor in the not very remote future. For that reason I have not taken any adequate measures to carry out the suggestions that were made at the last Regents' meeting in regard to establishing comprehensive reviews, but shall leave it to Dr. Pincoffs to make plans as he sees fit. We have, however, accepted a few short review articles covering the field of allergy in general, and allergy in reference to rheumatic fever in particular. Unless I receive more enthusiastic support from the Regents with regard to the publication of the medico-legal material by Hubert Smith, I shall not take the matter up further.

... On motion by Dr. Palmer, seconded and regularly carried, the report of the Acting Editor was adopted. ...

PRESIDENT IRONS: Next will be the report of the Committee on Fellowships and Awards, Dr. Francis G. Blake, Chairman.

DR. BLAKE: A meeting of this Committee was held at 2:00 p.m., November 17, with Dr. Jonathan C. Meakins, Dr. C. C. Shaw, as Educational Director, and Dr. Blake present. The Committee reviewed numerous applications for Research Fellowships and Clinical Fellowships, and reports as follows:

*Candidates for Research Fellowships:* The Committee approved the applications of the following candidate:

Kenneth Austin Evelyn, Montreal, Que., Canada—to work in the Department of Pathology, McGill University, under Professor Duff, and at the Royal Victoria Hospital under Dr. Jonathan C. Meakins on the Pathogenesis and Treatment of Hypertension. Stipend recommended, \$2,500.00.

*Candidates for Clinical Fellowships:* The Committee approved the applications of the following candidates:

Joseph Michael Barker, Arlington, Va.—to work with Dr. Frank Wilson, University of Michigan Hospital. Stipend recommended, \$3,000.00.

Norman Leo Cressy, Beverly, Mass.—to work in the Department of Medicine at Yale University under Dr. Francis G. Blake. Stipend recommended, \$3,000.00.

John Bamber Hickam, Dayton, Ohio—to work with Dr. Stead at Emory University. Stipend recommended, \$2,500.00.

John Scott Hunt, Lexington, Ky.—to work with Dr. Hugh J. Morgan at Vanderbilt University. Stipend recommended, \$2,000.00.

Philip Anthony Tumulty, Washington, D. C.—to work at the Johns Hopkins Hospital under Dr. Warfield Longcope. Stipend recommended, \$2,500.00.

. . . On motion by Dr. Blake, seconded and unanimously carried, the awarding of the above fellowships was approved and confirmed. Also on motion by Dr. Blake, seconded and unanimously adopted, it was RESOLVED, that four other applications for Research Fellowships and three other applications for Clinical Fellowships be declined. . . .

DR. BLAKE (Continuing): *The John Phillips Memorial Award, 1946*—No action has been taken by the Committee to date with respect to the John Phillips Memorial Award, but the usual list of individuals in the College will be circularized now in respect to recommendations for this Award, and as soon as replies have been received the Committee will report with respect to its recommendations. These will have to be submitted to the Executive Committee for action. Incidentally, the complete files on all the candidates for fellowships are available at the College Office, if any member of the Board wishes to examine them more in detail.

DR. PALMER: Does the recipient of the Phillips' Award have to be an M.D.?

DR. BLAKE: No. I think there have already been Awards to scientists who were not M.D.'s.

DR. BARR: May I ask the distinction between Research and Clinical Fellowships, as offered by the College?

DR. BLAKE: That is a pertinent question. All of these five men, to whom fellowships have been awarded, with the possible exception of one, in addition to wanting additional training in medicine, are types of individuals who will engage also in clinical investigation. To try to draw a sharp distinction between the five Clinical Fellows and the one Research Fellow, except for their particular field of interest, is perhaps difficult, except that it is the plan of all to engage in clinical work, as well as such research work as they may wish to do.

. . . In subsequent discussion, it was brought out that possibly the Clinical Fellowships are more of the character of residencies, whereas the Research Fellowships are clearly for research work. . . .

. . . On motion by Dr. Blake, seconded and carried, the report of the Committee on Fellowships and Awards was adopted as a whole. . . .

PRESIDENT IRONS: Next will be the report of the Committee on Educational Policy, Dr. Roger I. Lee, Chairman.

DR. LEE: This Committee met November 17, and those present included Dr. Irons, ex-officio, Dr. Waring of the Advisory Committee on Postgraduate Courses, and myself, with Dr. C. C. Shaw, the Educational Director. The Committee reviewed the program of Postgraduate Courses offered during the autumn of 1945, for which the registration was as follows:

Course	Associates	Fellows	Non-Members	Total	Army	Navy	U.S.P.H.S.	Civilians
No. 1	19	42	8	69	11	6	2	50
No. 2	15	30	14	59	23	0	2	34
No. 3	9	11	14	34	9	5	2	18
No. 4	26	64	0	90	9	0	3	78
No. 5	27	62	127	216	100	8	2	106
No. 6	25	40	43	108	51	3	3	51
No. 7	32	75	1	108	14	4	1	89
	153	324	207	684	217	26	15	426

The Committee, under new business, reviewed the proposed schedule of Postgraduate Courses for 1946. These courses were selected in view of the experience with past courses in popularity. It is desired not to overwork certain individuals in certain places. The proposed schedule is wholly tentative, but the Committee approves in general the courses outlined below and recommends to the Board of Regents that the Educational Director proceed, with the understanding that there will be, of necessity, changes and adjustments.

*Spring, 1946:*

1. ALLERGY—Massachusetts General Hospital, Boston—Dr. Francis M. Rackemann, Director.
2. CARDIOLOGY—University of Virginia Department of Medicine, Charlottesville—Dr. J. Edwin Wood, Jr., Director.
3. CARDIOLOGY—Woman's Medical College of Pennsylvania, Philadelphia—Dr. William G. Leaman, Jr., Director.
4. CHEMOTHERAPEUTICS—Washington University School of Medicine, St. Louis—Dr. W. Barry Wood, Jr., Director.
5. GASTRO-ENTEROLOGY—Graduate Hospital, University of Pennsylvania, Philadelphia—Dr. Henry L. Bockus, Director.
6. GASTRO-ENTEROLOGY—Mayo Foundation, Rochester—Dr. Walter C. Alvarez and Dr. E. H. Ryncarson, Directors.
7. GASTRO-INTESTINAL DISEASES—Massachusetts General Hospital, Boston—Dr. Chester M. Jones, Director, possibly in conjunction with a course in Pathology of Internal Diseases under Dr. Tracy Mallory, Director.
8. GENERAL MEDICINE—Emory University School of Medicine, Atlanta, Ga.—Dr. James E. Paullin, Director.
9. HEMATOLOGY—Ohio State University College of Medicine, Columbus—Dr. Charles A. Doan, Director.
10. INTERNAL MEDICINE—Harvard Medical School, Boston—Dr. James H. Means, Director.
11. INTERNAL MEDICINE—University of Minnesota Center for Continuation Study, Minneapolis—Dr. W. A. O'Brien and Dr. Cecil J. Watson, Directors.
12. INTERNAL MEDICINE—University of Texas Department of Medicine, Galveston—Dr. Charles T. Stone, Director.

13. INTERNAL MEDICINE—Stanford University Medical School, San Francisco—Dr. Stacy R. Mettier, Director.
14. PHYSIOLOGY OF DISEASES—Harvard Medical School, Boston—Dr. George Thorn, Director.
15. PSYCHIATRY AND NEUROLOGY—Institute of the Pennsylvania Hospital, Philadelphia—Dr. Edward A. Strecker, Director.
16. NEUROLOGY (an alternate for course above)—Northwestern University Medical School, et al, Chicago—Dr. Roland Parks Mackay, Director.

*Autumn, 1946:*

1. GENERAL MEDICINE—Johns Hopkins University School of Medicine and University of Maryland School of Medicine, Baltimore—with one director from each institution.
2. INTERNAL MEDICINE—McGill University Faculty of Medicine, Montreal—Dr. Jonathan C. Meakins, Director.
3. METABOLIC DISEASES AND NUTRITION—University of Cincinnati College of Medicine, Cincinnati—Dr. M. A. Blankenhorn and Dr. Tom D. Spies, Directors.
4. PERIPHERAL VASCULAR DISEASES—University of Pennsylvania School of Medicine, Philadelphia—Dr. Isaac Starr, Director.
5. PERIPHERAL VASCULAR DISEASES—Mayo Foundation, Rochester—Dr. E. V. Allen, Director.
6. PSYCHIATRY AND NEUROLOGY—University of Wisconsin Medical School, Madison—Dr. Hans H. Reese, Director.

Also submitted for consideration, some time in the distant future, was a course in General Medicine at the University of Mexico, at Mexico City, under Dr. Francisco de P. Miranda, Director.

The Committee discussed at some length an attempt to correlate these courses, because it appears there are various Fellows of the College, some of them distinguished Fellows, who like to see what is going on in other places and in various departments, some of them taking off two or three months to take courses in New York, Philadelphia, Baltimore, Chicago and the West. Experience thus far indicates that all these courses will prove desirable, and many of them will be oversubscribed. As the Executive Secretary has already said today, we should get the registration of these courses down "from a convention to a class."

. . . On motion by Dr. Lee, seconded and regularly carried, the schedule of proposed courses was approved; likewise, the report as a whole was approved. . . .

MR. LOVELAND: I wish to obtain the advice of the Regents with regard to the registration fees for these courses—from members, from non-members and from those in the Armed Forces. Throughout the War no charge whatsoever has been made to a man on active duty in the Armed Forces. This applied both to members and non-members. However, we took non-members only when accommodations were adequate to admit them. How much longer shall the registration fee be waived for members of the Armed Forces? Members? Non-members? We have observed that those to whom we give waiver of the registration fee have not been as careful to notify us when they are unable to attend a course. Perhaps they have not attached great importance to this, even though we have emphasized the necessity of sending in cancellations in advance, so that other physicians could be accommodated. This may be due to the fact that things that come free usually are not evaluated as worth very much. From a practical standpoint, not financial, I have wondered if there should not be at least some small charge, possibly a half of the usual fee, to the men on military service in the future.

PRESIDENT IRON'S: May we have discussion by the Regents?



DR. WALTER B. MARTIN: I believe there should be a fee. I think it is bad to admit these men entirely without fee to courses of this kind. A nominal fee would be appropriate.

DR. LEROY H. SLOAN: I do not think the fees charged at present are high enough for what the men are getting. I am in favor of raising the fees generally.

DR. LEE: I should hope that whatever action is taken will be tentative; there may well be a nominal fee, but now that Dr. Shaw has become the Educational Director and has to get his initial experience, more information will come later. There may be quite a different situation in the next few months.

DR. SLOAN: There should be further consideration given to the size of these courses. Let us not make a huge meeting out of a postgraduate course.

. . . On motion by Dr. Sloan, seconded and adopted, it was RESOLVED, that the question of nominal fees, or other fees, for postgraduate courses be left to the Executive Secretary and the Educational Director, under the direction of the Committee on Educational Policy. . . .

PRESIDENT IRONS: May we have the report of the Committee on Post-War Planning for Medical Service, Dr. George Morris Piersol, Chairman.

DR. PIERSOL: The Committee met yesterday at 6:00 p.m., with the Educational Director. You will recall a letter was sent to the Regents and Governors, asking them to submit data and information in regard to various available appointments, residencies, etc. This letter brought little results. Many answers were received, but few facilities are available. The demand for residencies and postgraduate training on the part of returning veteran members of the College far exceeds any available facilities.

Information collected by the Bureau of Information of the American Medical Association and cataloged by that Bureau according to counties throughout the country has been made available by the various State and County medical societies, and all Reserve Medical Officers on active duty have been advised. The College is not in a position to operate a placement service, and has been unable to guarantee any adequate amount of information to help any large proportion of the returning veteran members of the College. The best we can do is to refer these individuals to the Bureau of Information of the American Medical Association.

The Committee was in favor of circularizing deans of medical schools and postgraduate schools to obtain further information in planning a broad educational policy for the College. At present our activities are largely confined to carrying on our graduate courses.

. . . On motion by Dr. James E. Paullin, seconded and carried, the above report was adopted. . . .

PRESIDENT IRONS: May we have a report from the American Board of Internal Medicine? In the absence of the Chairman, Dr. Reginald Fitz, we will hear from Dr. James J. Waring.

DR. WARING: My report has been prepared by the very active and very efficient Secretary-Treasurer, Dr. William A. Werrell, of Madison.

Total receipts, from January 1 to October 31, 1945, are \$16,000.00, which, with a holdover balance of about \$3,000.00 amounts, in round figures, to \$19,000.00 on deposit as of October 31, 1945. Disbursements to this date, October 31, 1945, \$13,800.00, leaving a balance of about \$5,200.00. Summary of the funds in hand include \$40,000.00 in U. S. Savings Bonds and \$7,000.00 in savings accounts in three different banks, with a balance on deposit in the Madison Trust Company, amounting to a total, as of October 31, 1945, of \$57,000.00.

The total number of physicians certified, with special oral examinations conducted by Colonel William S. Middleton in the European Theater, 37; additional certifications in this country, May 22, June 8 and June 13, bring the total up to 303 certified by examination; 12 were certified without examination; total certifications, 315. Cer-

tifications in the sub-specialties: Allergy, 5; Cardiovascular Diseases, 13; Gastro-entology, 9; in the sub-specialties without examination, 4; total certifications in the sub-specialties include 5 in Allergy, 13 in Cardiovascular Diseases, 12 in Gastro-entology, 12 in Tuberculosis. Written examination data: February 19, 1945, 168 passed and 43 failed; 9 papers are not yet graded; grand total, 220. Written examinations held October 15, 1945: approximately 302 took the examination, but papers are not yet graded. The oral examinations scheduled to be held in San Francisco in the autumn had to be cancelled, because no hotel accommodations were available due to the arrival of the Pacific Fleet.

Dr. Werrell points out, in regard to the financial report, that the surplus is more apparent than real, because there is going to be a total of 407 candidates eligible to take the oral examinations in 1946, and this will be an expensive program. Dr. Werrell has also included herewith a spot map, showing the number of candidates and their locations over the country, eligible for the first, second and third oral examinations.

. . . On motion by Dr. David P. Barr, seconded and carried, the report was adopted. . . .

PRESIDENT IRONS: I would like to commend again Dr. Werrell, who is a most efficient operating secretary of whom we are all very appreciative.

Next will be the report of the Committee on Finance, Dr. Charles F. Tenney, Chairman.

DR. TENNEY: The Finance Committee met yesterday afternoon and reviewed in detail the operating statements prepared by the Executive Secretary for the year 1945, with estimations for November and December. A copy of these statements and comparisons are placed in your hands. You will find that the College operated below the budgets approved by the Board of Regents, and you will also note that the income was greater than estimated a year ago. This was largely due to increased income from subscriptions and advertising in the ANNALS OF INTERNAL MEDICINE, and to additional Life Members.

The Committee likewise surveyed in detail the proposed budgets, copies of which are in your hands, and recommends to the Board of Regents their adoption, with the addition of a total of \$500.00 on the Executive Secretary's budget to provide an honorarium to the Treasurer's secretary and an honorarium to the Executive Secretary's secretary, and an addition of \$75.00 for honoraria to two secretarial assistants in the Acting Editor's Office.

The Finance Committee reviewed recommendations received from the investment counselors, Drexel & Co., and within authority already vested in the Committee by the Board of Regents, has taken appropriate action with regard to the General Fund Account. The Committee, however, desires to obtain the approval of the Board of Regents in the following transactions concerning securities and investments in the Endowment Fund; to wit: authorization to proceed as follows:

(1) To invest approximately \$3,800.00 of the Endowment Fund surplus cash in securities to be selected from later recommendations of the investment counselors;

(2) To sell \$5,000.00 Great Northern Railway Company Bonds and \$5,000.00 Pennsylvania Railroad Company Bonds, as recommended by the investment counselors, and to re-invest the proceeds for the Endowment Fund in acceptable securities later to be recommended by the investment counselors. These particular bonds were purchased at 89.27 and 100.26, respectively, and their present market prices are 121 1/8 and 126, respectively. It should be recorded that the investment counselors have already made recommendations for the investment of these funds, which, in the opinion of the Finance Committee, after careful consideration, are not wholly acceptable, and the Committee, therefore, is requesting other recommendations.

. . . On motion by Dr. Walter W. Palmer, seconded and regularly carried, the above report was adopted and approved. . . .

DR. WARING: In my report on the American Board of Internal Medicine, I referred rather casually to the oral examinations conducted by Colonel Middleton in the European Theater. Colonel Middleton's contribution was a most important one for the prestige of this organization and meant a great deal in the way of convenience and accommodation to the men individually concerned. I think more adequate recognition of that should have been made in my report.

PRESIDENT IRONS: In that connection, it has already been reported to the Board that the Board of Internal Medicine received very active coöperation from the Surgeon General, and that written examinations were held all over the world—North Africa, Australia, India and in other places, as well as in almost all of the larger military centers in this country. The holding of these examinations has been a very definite morale builder for a great many Medical Officers. They felt that everything they had done up to date had not all gone to waste. In the case of the oral examinations, however, in some other localities, we had no member of the American Board available, and it was felt that the Board could not delegate oral examinations to anyone, unless such examinations could be carried out under the medical direction of a member of the Board. That is not in disrespect of the ability of other Medical Officers who might conduct such examinations, but the Board had a definite responsibility that could not be delegated to others. Colonel Middleton was uniquely situated, and he did a most commendable job.

Next is the report of the Treasurer, Dr. William D. Stroud.

DR. STROUD: The Treasurer's report is supplementary to the report of the finance Committee the Board has already received. At the conclusion of the year, the accounts of the College will be verified by a public accountant, final financial reports prepared and presented to the Board of Regents.

It has probably already been drawn to your attention, through the financial statements already presented, that during 1945 certain appropriations were not used, because of restrictions due to the War. Referred to are the Regional Meetings of the College, which were curtailed by ODT regulations, and appropriation for a joint meeting of the Regents, Governors, and a few other minor items. Obviously, the appropriation for the Educational Director was not intended to be expended in its entirety in 1945, because it was clearly understood that the office would be established later in the year. The surplus anticipated for December 31, 1945, a grand total of approximately \$39,000.00, is very much greater than was anticipated a year ago, but \$15,000.00 of this belongs to the Endowment Fund and may not be expended, and the balance is the result of curtailment of activities occasioned by War restrictions.

The finances of the College are in wholly satisfactory condition, and we may look forward to increased income in the future. It seems appropriate that the Board of Regents authorize the extension of certain activities as an immediate post-war program, and that we draw moderately upon the Surplus Account of the College set up in previous years. This should not, however, be a precedent for continued overdrawing of the current income in years to come, for reasons that are obvious to all.

A survey of the College portfolio reveals that the Book Value of all holdings on November 7, 1945, was \$317,511.12, whereas the Cash Value on that date was \$354,083.75, showing an appreciation of \$36,572.63. Our current yield on securities in the Endowment Account is 3.05%, and on the General Account 3.77%, or an average for the entire investment account of 3.36%. Our highest rate of income is from preferred stocks, 4.03%; on common stocks, the rate is 3.71% and on bonds, 2.93%. The College already holds in its portfolio \$117,400.00 in United States Savings Bonds, on which the income is 2½%; this, naturally, has the effect of lowering materially the average rate of income.

We consider the services of our investment counselors, Drexel & Co., efficient and wholly satisfactory.

... On motion by Dr. George Morris Piersol, seconded and carried, the report of the Treasurer was adopted. . . .

PRESIDENT IRONS: We are faced with some very large and difficult problems in the matter of re-education assistance to returning Medical Officers, members of the College, and I would feel very much in favor of all measures possible for the continuing support of the College in this most important program. I think, however, we must be cautious in over-expending our surplus. There will come a time when the College will be very glad that it has been able to build up as large a surplus, or even a larger one, because when you go down the street with nothing in your pocket you are very likely to accept almost any kind of a proposition to get a bite to eat, whereas if you have money in your pocket your moral sense is very much more to the fore. Then you can throw out your chest. I am impressed with the importance of maintaining and building up a substantial reserve in the College. I say that because there is a tendency now and then to get emotional, quite properly so, but our emotions sometimes override our judgment in the expenditure of funds.

We have now concluded the Committee reports on the agenda. Dr. Meakins, will you elaborate on your all-American problem?

DR. JONATHAN C. MEAKINS: Mr. Chairman, I feel that in the years to come the eyes of many people will turn to North America for medical education, and we are restricted as to whom we may take in as Fellows, or who may be eligible as Fellows. I am wondering if a situation might arise like this: a man came from Australia, took the examinations of the Board of Internal Medicine and then sought to become a member of the College. The present policy of the College is to exclude physicians who are not bonafide citizens of some North American Country. The man I am speaking about might establish residency in this Country for some time, he might become an Associate and then return to Australia. Would he then be ineligible, no matter how good he be, to become a Fellow? In other words, I feel personally that the American College of Physicians, on account of the War, and our members being scattered all over the globe, has made a very distinguished name for itself. I believe men in other Countries would like to become Fellows.

PRESIDENT IRONS: This is an important matter. There is much to be said on either side. Possibly we might consider honorary Fellowships, or something similar thereto, which would not imply supervision, or too much responsibility, for the man who had been so admitted.

MR. LOVELAND: It is not officially written into the By-Laws of the College that only citizens of North America shall be admitted to the College, but it has been a policy of the Board of Regents and the Credentials Committee to discourage the admission to the College of physicians who are not citizens of this Continent, or who neither speak nor read English. Such a person would not be able to participate in our meetings, to read our journal or to give or receive the usual benefits of membership. The only value of his membership to him would be the use of the designation "F.A.-C.P." Only yesterday there was a candidate from Brazil, who was sponsored by some of our New York Fellows, but election was denied, because of this previous principle adopted by the Board of Regents. If we were to extend College membership beyond North America, the By-Laws would have to be changed in those sections affecting the method or machinery of admission. A candidate must be proposed and seconded by Fellows of the College and endorsed by the College Governor for his territory. Naturally, we have no Governors outside of North America and our dependencies.

DR. PAULLIN: There is no provision for honorary members.

DR. WARING: I am interested in this matter, and I am quite in favor of extending College membership in some manner which would have to be seriously weighed by the Board of Regents, the Officers and the Credentials Committee, but I think there is a definite movement in the way of our extending the knowledge of what the American

medical profession is doing further and further to the South. For instance, the American Review of Tuberculosis, which has a very fine record and reputation throughout the English-speaking world, now publishes a summary of its articles in Spanish, as well as in English. There is another organization that has vigorously attempted to extend its membership south of the border. I mention this only to indicate there is definitely a tendency to try to bring physicians in Central and South American Countries into the sphere of American medical influence, and I think it is not a bad idea in this age when co-operation with other Countries is vitally important to our peace and future prosperity.

PRESIDENT IRONS: This question may be referred to the Public Relations Committee as a matter for report at the next meeting of the Board.

. . . On motion by Dr. David P. Barr, seconded and carried, the matter was so referred. . . .

PRESIDENT IRONS: Before luncheon we might discuss a few special problems and topics. Mr. Loveland, will you present the matter concerning Masterships?

MR. LOVELAND: Mr. President, in past years, as you know, the College has sporadically conferred a few Masterships. There has been no system in particular. These Masterships have been conferred primarily in appreciation and recognition of some great service, or services, to the College. We have had a good many such men, but we have recognized but few. It has occurred to me often, especially this past year, that there have been certain men who have in years gone by, and for many years, performed signal service who deeply merit recognition of their great contributions to the College. I haven't any prepared list, but I have already suggested to Dr. Irons that there should be a committee or agency in the College that would periodically review the question of recognition by Mastership of Fellows who have made the most worthy contributions to the College during the past many years, and who heretofore have not been recognized. I believe it a mistake to let these men go unnoticed until infirmities of body or mind would make it questionable whether Masterships should then be conferred. I have in mind one man who through two decades made great contributions to the College and who today is wholly disabled and is retired from practice, yet who should have been recognized long ago. There are other men whose contributions to this College are recognized by all men who are still active, to whom a Mastership would be a small recompense for their outstanding work in the College and their position in American Medicine.

. . . President Irons, in the absence of further discussion of the subject, passed on to a discussion of the policy of the College with regard to continuation of Regional Meetings. . . .

MR. LOVELAND: During the War, as you all know, the Regional Meetings held throughout the Country were the means of keeping the College active and alive in a real way. Members liked these Regional Meetings; the Governors organized fine programs, and the programs improved with experience. There may be a popular demand for continuing Regional Meetings regardless of our return to the Annual Session of the College. Before the War, the Regional Meetings were largely State Meetings, conducted for a single State. During the War, they became multi-State meetings, with from three to seven States combining. Regional Meetings, of course, cost money, and there is no financial return from exhibits. To continue this program as it has been conducted in the past year would cost at least \$7,500.00 a year. There is no such appropriation on the budget for 1946. The Executive Office ought to have the advice of the Regents concerning the policy for the future, when a Governor or a group of Governors inquire about organizing future Regional Meetings.

PRESIDENT IRONS: The Chair has felt that the development of Regional Meetings, necessitated in part by the War and our failure to be able to hold the general meetings, has been one of the great benefits the College got out of the War. These Regional

Meetings have been tremendously helpful in maintaining interest in the College, and certainly they could be continued and developed further.

DR. STROUD: I have heard some discussion of this subject, and the point has been raised whether, if Regional Meetings be continued or extended, they would not directly affect the attendance at the general Annual Meetings. It seems to me the Regional Meetings will stimulate rather than detract from the Annual Session.

PRESIDENT IRONS: Nowadays we would not object if the Annual Sessions were a little smaller.

DR. PIERSOL: How much liability should the College assume for these meetings?

PRESIDENT IRONS: Perhaps they could be almost self-supporting?

MR. LOVELAND: They have not been self-supporting, because the College must publish programs, furnish postage, carry on a large amount of correspondence and bear local expenses. Not one of the Regional Meetings has been conducted without a deficit. In fact, the College agreed to meet deficits up to \$250.00, but in some instances that has not been anywhere near adequate. The program committee of Regional Meetings has often wanted to invite distinguished guests, whose travel expenses must be met. Furthermore, these Regional Meetings cannot be as wholly under the direction of the Executive Office as is true of the Annual Sessions. More responsibility must be delegated to the Governors conducting the meetings.

PRESIDENT IRONS: Even at that, I should think the investment would be a good one.

DR. SLOAN: The Executive Offices might take a broader responsibility for these Regional Meetings, and more effectively thereby reduce the expense. Our experience in the past years will show where losses arose, and with care and direction to the General Chairman the expense could be reduced to a minimum. I would like to see the Regional Meetings kept up, perhaps, at a time of year not near that of the Annual Session. They will prove of real service to the College.

DR. PAULLIN: Could we provide \$5,000.00 in the budget for that expense?

MR. LOVELAND: For 1946 we are already drawing upon the surplus from former years by approximately \$20,000.00. That is because of an extended program for our educational department and the appointment of an Educational Director.

DR. PAULLIN: Could this \$5,000.00 be absorbed in the educational program?

MR. LOVELAND: A part of it could, perhaps. On our 1946 budget for the Educational Director there appears an item of \$2,500.00 for Postgraduate Courses. I believe the courses could be managed so that the cost to the College would not be that much. I am frank to say that I question the propriety of expending the tuition fees in the manner that some of the directors do.

DR. BARR: In the estimate for expenses and income for 1946, the budgets contain no item for income from commercial exhibits.

MR. LOVELAND: That matter was discussed in the Finance Committee meeting. In the first place, the Board of Regents had not previously directed that there would be an Annual Session, and we had not prepared a budget therefor. However, the income from the exhibits, if we resume the Annual Session in a large eastern center, should be adequate to pay the expenses of the meeting. There was discussion of this in the Finance Committee; a budget was not prepared; it was decided that if the Board of Regents authorize an Annual Session, that budgetary provisions for expenses should be made out of estimated income from the exhibits. I believe that this can be done. Our experience before the War was that our annual meetings cost approximately \$13,000.00 and that our exhibits produced a net income varying from \$12,000.00 to \$14,000.00. However, when we met in St. Paul in 1942 there was a deficit of \$3,000.00 on the annual meeting, but that was due to the location and the reduced size of the Technical Exhibit.

DR. CHARLES T. STONE: It seems to me that we ought not to abandon the Regional Meetings entirely in 1946, for the simple reason that even though the Annual Session

is held, the difficulties in transportation and hotels will considerably reduce our attendance, and those who cannot come to the annual meeting will want to attend some Regional Meeting later on. Isn't it a part of our responsibility to give these members some sort of a meeting in the area in which they live? It occurs to me, in connection with the expense of Regional Meetings, that it might be possible to have a nominal registration fee that would largely take care of the expense. I think the Finance Committee, of which I am a member, probably would be unwilling to dip into the permanent funds any more than already provided in 1946.

PRESIDENT IRONS: The Chair understands from the tenor of the discussions that it would be the wish of the Regents to have the Executive Secretary continue to encourage Regional Meetings and in a tactful way to intimate that they shall be self-supporting, as far as possible.

DR. LEE: I think it would be of much importance to have some central control over these Regional Meetings, this central control to be depended upon for financial assistance as well as getting out their programs and the like. In the beginning I was somewhat skeptical about these Regional Meetings, but I have changed my mind. I think they are very valuable. On the other hand, there is always a tendency—and I have looked over some of the Regional Meetings—that local committees may go a little far and wide in getting some of their speakers and drifting toward substituting a local annual session for a Regional Meeting. The control the central office can establish is very important; guest speakers should come from the region and not from the country at large.

PRESIDENT IRONS: I have a report from Dr. Francis F. Borzell, who is unable to be present. The War-Time Graduate Medical Meetings will close as of December 31, 1945, and the physical equipment, files, etc., will be turned over to the College as a small gesture because of the courtesies extended to the Committee by the College in its headquarters and also for the personal services of the Executive Secretary. Furthermore, Dr. Borzell wishes to inform the Board that enough finances are on hand to complete the work, and that any balance will be distributed pro rata among the three organizations sponsoring the War-Time Graduate Medical Meetings. Dr. Borzell extends his personal appreciation to the Board of Regents.

. . . A motion to accept the report of Dr. Borzell, with deep appreciation for his services, as well as for those of Dr. Edward L. Bortz, was made by Dr. William D. Stroud, seconded and unanimously adopted. . . .

#### LUNCHEON RECESS

PRESIDENT IRONS: The next item on the agenda is the consideration of resumption of the Annual Session of the College. That involves whether or not we shall have such a Session and, if so, the place, date and General Chairman.

DR. PAULLIN: I move we have an Annual Session in the spring of 1946.

. . . Motion was seconded and adopted. . . .

PRESIDENT IRONS: Where shall the Annual Session be held?

DR. PAULLIN: I move we meet in Philadelphia, where we were to have met in 1943.

. . . Motion was seconded and regularly adopted. . . .

PRESIDENT IRONS: On what date shall the Session be held?

MR. LOVELAND: Dr. Piersol, I, and others, have investigated the dates when facilities will be open in Philadelphia. We have also taken into consideration the dates of other meetings, including that of the Philadelphia County Medical Society's Postgraduate Institute. Easter falls on the 21st of April. We should not want the meeting during the week preceding or immediately following Easter. The Association of American Physicians will meet in Atlantic City on May 28 and 29; the American Medical Association is expected to meet in San Francisco during July. While the College has never

met as late as May, we would like to have that possibility considered. Philadelphia is lovely in May. April is oftentimes a nice month and oftentimes it is not. It would be ideal, from the standpoint of weather, during May, and we might readily consider a date near enough to that of the Association of American Physicians, to enable those from distant points in the West to come East, attending both meetings during one trip. The particular weeks that are open for discussion and consideration are the week of April 29 and possibly the week of May 13, or May 20, the latter being the week immediately preceding the Association's meeting in Atlantic City.

. . . There was general discussion entered into by all. It was pointed out that the week of April 29 conflicts with the Postgraduate Institute of the Philadelphia County Medical Society's meeting, already scheduled. . . .

. . . On motion by Dr. James E. Paullin, seconded and carried, it was RESOLVED, that the time of the meeting be referred to the President, the Secretary-General and the Executive Secretary. . . .

DR. WARING: I would like to suggest to the Committee on Postgraduate Courses that they consider the advisability of the sequential arrangement of local Postgraduate Courses and the Annual Meeting. In other words, men coming from a distance might be glad indeed to attend both a College Postgraduate Course in this area and also the Annual Meeting.

PRESIDENT IRONS: Whom do you suggest as the General Chairman of the Philadelphia Annual Session?

DR. PAULLIN: The same one who was elected before to be the General Chairman, had we held our meeting here in 1943, Dr. George Morris Piersol.

PRESIDENT IRONS: There appears to be a general feeling among the Regents that Dr. George Morris Piersol shall be asked to continue his work as General Chairman.

DR. PIERSOL: I shall be very glad to serve.

PRESIDENT IRONS: Next, may we discuss the nature of this meeting? What shall we do with regard to its general outlines? Shall we hold a Victory Convocation?

MR. LOVELAND: From the outbreak of the War, I think we have emphasized that when the War is over and we can resume our Annual Meetings, the Convocation for the induction of Fellows shall be organized as an especially impressive occasion. There will probably be a thousand Fellows to be inducted, and it is hoped that the great majority can be present. We thought it appropriate to call the next Convocation the "Victory Convocation."

PRESIDENT IRONS: Resuming the Annual Sessions will also take care of the election and installation of new Officers, Regents and Governors, which will take place in accordance with provisions of the Constitution and By-Laws.

We should authorize a meeting of the Committee on Credentials about one month in advance of the Annual Session, so that most of the Committee's work can be concluded in advance.

Are there any other items that should come before the Board at this time.

DR. PAULLIN: Mr. Chairman, before we adjourn, I think the Board of Regents ought to extend to Mr. Loveland a vote of thanks for what he has done and for the untiring effort he and his staff have made during these last years. They have been very unselfish, and we should recognize it by extending a vote of thanks.

. . . The Regents all rose in an expression of thanks. . . .

. . . The meeting *adjourned* at 1:45 p.m. . . .

Attest: E. R. LOVELAND,

Secretary



## OBITUARIES

## DR. JOHN MINOR BLACKFORD

Dr. John Minor Blackford died September 12, 1945 at the Virginia Mason Hospital in Seattle, Washington. Dr. Blackford became ill Saturday, September 8 on arriving home from a trip to Alaska.

Son of Launcelot and Eliza Blackford, he was born February 1, 1887 at Alexandria, Virginia. Educated in that State, he received his medical degree in 1910 from the University of Virginia and served his internship at the University of Virginia Hospital. He served on the staff of the Mayo Clinic at Rochester, Minnesota from 1911 until 1917 after which he came to Seattle, Washington.

In 1918, with the late Drs. James Tate Mason and Maurice F. Dwyer, Dr. Blackford helped found the Mason Clinic and later, in association with them and others, built the Virginia Mason Hospital. His imagination and ability as an organizer were major factors in the later enlargement of the Hospital and improvement of its services. To the institutions of the Virginia Mason Hospital and the Mason Clinic, he gave liberally of his energy and enthusiasm up to the time of his death.

Dr. Blackford was the author of many articles in medical and scientific journals and was a member of the Washington State Medical Association, the King County Medical Society, American Medical Association, American Gastroenterological Association, the North Pacific Society of Internal Medicine, Fellow of the American College of Physicians, and Diplomate of the American Board of Internal Medicine.

In January, 1927, Dr. Blackford, Dr. George F. Strong, and Dr. Frederick Epplen met in Spokane, Washington and conceived the idea of an association of internists in the Pacific Northwest. At an organization meeting in Seattle, April 24, 1927, these three men selected a group of 19 internists, including themselves, as founders of the North Pacific Society of Internal Medicine.

Surviving Dr. Blackford are his widow, Mrs. Elizabeth Mann Blackford at the family home, 4318 55th Avenue N.E.; a son, Commander William Mann Blackford, Executive Officer at the Great Lakes Naval Training Station; two daughters, Mrs. J. Newton Morris and Mrs. Marvin McClatchey, Jr., of Seattle, and four grandsons.

His outstanding medical ability and judgment, which early placed him among the leaders of the medical profession in the Pacific Northwest; his observations and contributions to medical literature; his sterling character, which attracted the support of his medical confreres and business associates, are apparent. His ideal family life, his association of over twenty-five years in a professional partnership which notoriously requires a maximum of fairness and the ability to compromise, his kindness of character and the warmth of his personality, produced in professional contacts a large pro-

portion of warm personal friends. Rarely indeed can a man in any station of life lay down his burdens at his time of life and have the void which his passing creates so completely filled with the loving memories of his family and the appreciation of his friends. To each of his associates and to his patients his death is a personal loss.

E. G. BANNICK, M.D., F.A.C.P.,  
Acting Governor for Washington

### DR. TOM LOWRY

In preparing this obituary of Dr. Tom Lowry, M.D., F.A.C.P., Dean of the University of Oklahoma School of Medicine, it is quite unnecessary to speak in laudatory terms to those who knew him. Dr. Lowry was exceptionally naive in making friends and in keeping them. He was a man among men. Respected because of his ability in his chosen profession, his sterling qualities as a man, about whom no one could say aught but good concerning his character, friendly manner, and religious background. Endowed with an unusually fine voice, he and his brother responded generously in singing alone or with a quartet. Strong of muscle and fleet of foot, these brothers were known for their prowess in athletics. Their versatility was remarkable.

In writing of Dr. Tom, it would be amiss not to speak also of his identical twin brother, Dr. Dick, who succumbed in the same dramatic way four years ago. Two brothers could not have been more alike in stature, looks and accomplishment. His father, his older brother, and his twin brother all were victims of coronary occlusions. Dr. Tom often spoke of his impending doom, but his fortitude and equanimity were marvelous. With this in mind, he gave up a large and lucrative practice, following his brother's death, and accepted the Deanship of the University of Oklahoma School of Medicine. Previously he had been occupying the Chair of Clinical Medicine. The morning after his election as Dean he was stricken with a coronary episode which laid him up for several months, and thereafter he was able to devote only a few hours a day to the Deanship.

Dr. Tom lived in Oklahoma most of his life; he graduated from the Oklahoma University at Norman with a B.S. degree in 1914, and an M.D., 1916. Having acted as councillor for his district in the Oklahoma State Medical Association, the horizon of his activities was broad, enabling him to be of great value to the betterment of medicine. He served as a Captain in World War I and was with the 24th Evacuation Hospital in France. Thereafter, in 1924, he pursued a course at the Colorado School of Tuberculosis.

He was a member of his County and State Medical Societies and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1929. He was certified by the Ameri-

can Board of Internal Medicine; a member of the Methodist Church; a Rotarian; a member of the Phi Beta Pi Medical Fraternity; a member of the Phi Beta Kappa National Scholastic Fraternity; a member of Phi Mu Alpha Biology Group; Pe-et, because of being the outstanding freshman at the University; and he received the Litzeiser Medal as an outstanding senior.

Dr. Tom was stricken with the second coronary episode after a night call to his aged mother and died the same day, December 11, 1945. His remains were interred in Memorial Park Cemetery among a large concourse of friends. He is survived by his mother, wife, and three daughters: Mrs. Robert Wallace King, a granddaughter Sheryl Lou King, of New York City; Miss Jean Lowry, a student at Columbia University; and Miss Elizabeth Ann Lowry, at the University of Oklahoma.

LEA A. RIELY, M.D., F.A.C.P.,  
Governor for Oklahoma

### COLONEL HARLEY JAMES HALLETT, (MC), U. S. A. (RET'D)

Colonel Harley James Hallett, F.A.C.P., Lake Wales, Florida, died suddenly on December 11, 1945, of coronary occlusion.

Colonel Hallett was born at McLean, Illinois, September 16, 1880. He graduated in medicine from the Jefferson Medical College of Philadelphia in 1905 and early entered the Medical Corps of the United States Army. For many years he was Chief of the Medical Service at the Army and Navy General Hospital at Hot Springs, Arkansas. He attained the rank of Colonel in March, 1937. He had fulfilled numerous assignments in the Army including Post Surgeon and Commanding Officer at the Station Hospital, Fort Devons, Massachusetts, and Post Surgeon, Fort Kamehameha, Honolulu, T. H. He retired from active duty on November 30, 1940, and for the past few years had been residing at Lake Wales, Florida.

Colonel Hallett was a member of the American Medical Association and had been a Fellow of the American College of Physicians since 1930. He was a man of splendid professional qualifications and his passing is recorded with deep regret. He is survived by his wife, Mrs. Helen M. Hallett, Lake Wales, Florida.

### DR. BENJAMIN WARREN BLACK

Benjamin Warren Black, M.D., F.A.C.P., passed away at his home in Oakland, California on December 1, 1945. Born in Fillmore City, Utah, May 21, 1887, Dr. Black spent his early life in Utah and received his pre-medical training at the University of Utah; also at the University of Chicago, receiving his M.D. degree in 1916 from the Medico-Chirurgical College of Philadelphia. He had an active and interesting career, serving in World War I in the United States Army from 1917 to 1919. He was

Regimental Surgeon with the rank of Major, serving with the 157th Infantry. At the time of his death he was a Lt. Colonel in the Medical Reserve on inactive status. From 1920 to 1921 Dr. Black was with the U. S. Public Health Service. From 1924 to 1926 he was Executive Officer with the U. S. Veterans Bureau, and Medical Director of the U. S. Veterans Bureau from 1926 to 1928. From 1928 to the time of his death, he served as Medical Director of Alameda County; also serving as medical-legal advisor to the District Attorney's office, Alameda County. He was a member of the Board of Directors of the First Federal Savings and Loan Association, of Oakland. Dr. Black was President, 1940 to 1941, of the Oakland Forum. He was President in 1940 of the American Hospital Association; Director in 1940 of the Western Institute of Hospital Administration. He was a Fellow and former Vice-President of the American College of Hospital Administrators. He was a member of the American Association for the Advancement of Science, Association of Military Surgeons of the United States, the California Academy of Medicine, Fellow of the American Psychiatric Association, and American Medical Association. He became a Fellow of the American College of Physicians in 1927.

Dr. Black contributed numerous articles to the medical literature, being interested chiefly in hospital administration and psychiatry. He was an active and very interested Fellow of the College. His civic activities included the following: Trustee of the Kiwanis International; a thirty-third degree Mason, including Scottish Rite (Master 1940) and Shrine; member of the Commonwealth Club and Claremont Country Club. One of his chief means of recreation was golf.

Dr. Black is survived by his widow, Mrs. Jean Black, and a daughter, Margaret Black Kockritz; also a son, Benjamin Marden Black, M.D., a surgeon at the Mayo Foundation in Rochester, Minnesota.

Dr. Black held a very important hospital administrative position in Alameda County. His special ability as an organizer did much to build up the Alameda County hospitals. He was always very much interested in younger doctors, great numbers having passed under his influence as a hospital administrator. His advice and assistance helped many to secure a start after leaving hospital training.

ERNEST H. FALCONER, M.D., F.A.C.P.,  
Governor for Northern California

### DR. LAWRENCE JOSEPH RIGNEY

Lawrence Joseph Rigney, M.D., F.A.C.P., Wilmington, Del., died November 28, 1945, in the St. Francis Hospital after a long illness.

He was born February 19, 1890; received his pre-medical training at the University of Delaware; M.D., 1920, University of Maryland School of Medicine; was Chief Resident Physician of the Bayview Hospital in

Baltimore; postgraduate work on numerous occasions at the University of Pennsylvania; served as Instructor in Medicine, 1930-1941, in the University of Pennsylvania School of Medicine. Since 1933, Dr. Rigney had been Chief of Medicine, Gastro-intestinal Clinic, St. Francis Hospital, Wilmington, and a member of the Staff of the Delaware Hospital. He was the author of several published papers, and formerly served as Vice-President of the New Castle County Medical Society. He was a member of the Delaware State Medical Society and the Delaware Academy of Medicine; a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1941.

LEWIS B. FLINN, M.D., F.A.C.P.,  
Governor for Delaware

### DR. MILLS STURTEVANT

Dr. Mills Sturtevant, F.A.C.P., died on October 29, 1945, of pneumonia.

He was born in Whitefield, New Hampshire, in 1882; attended Manchester, New Hampshire, public schools; A.B., 1904, Dartmouth College; M.D., 1908, Columbia University College of Physicians and Surgeons; Interne, 1908-1910, Bellevue Hospital; Resident Physician, 1910-1913, Louisa Minturn Hospital; Visiting Physician, 1913-1919, and Chairman of Board of Trustees, 1918, of same institution; Assistant Visiting Physician, 1913-1918, Willard Parker Hospital; Visiting Physician, 1915-1917, Central and Neurological Hospital; for many years Visiting Physician in charge of gastro-enterology, Bellevue Hospital, and in later years Consulting Physician at Bellevue Hospital; Professor of Clinical Medicine, New York University College of Medicine; member of his County and State Medical Societies, the Harvard Society, the Quiz Medical Society, Manhattan Medical Society, Bellevue Alumni Society, and American Gastro-enterological Society; Fellow, New York Academy of Medicine, American Medical Association, and American College of Physicians, the latter since 1920; author of numerous published papers; Diplomate, American Board of Internal Medicine.

Dr. Sturtevant had been an active and enthusiastic Fellow of the College since 1920 and had been a Life Member since 1937.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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## PENICILLIN TREATMENT OF EMPYEMA: REPORT OF 24 CASES AND REVIEW OF THE LITERATURE \*

By BRUCE BROWN, M.D., EDWIN M. ORY, M.D., MANSON MEADS, M.D.,  
and MAXWELL FINLAND, M.D., F.A.C.P., *Boston, Massachusetts*

It is generally conceded that the sulfonamide drugs have not been successful in effecting cures in cases of empyema once frank pus has developed in the pleural cavity. The most that can be expected from these drugs is a reduction in the incidence of empyema when they are properly used in the treatment of pneumonia, a reduction in mortality in operated cases and possibly the cure without open drainage of an occasional empyema that is treated very early.<sup>1-10</sup>

Certain properties of penicillin as a therapeutic agent suggest that it should be more useful than the sulfonamides in cases of empyema. The organisms most frequently associated with empyema, namely, pneumococci, hemolytic streptococci, staphylococci, anaerobic streptococci, fusospirochetes and some others are much more susceptible to penicillin than to sulfonamides. Most of the gram-negative bacilli, including *Hemophilus influenzae* and *Klebsiella pneumoniae* (Friedländer's bacillus) are not susceptible to penicillin, but they are infrequent causes of empyema, nor are they highly susceptible to sulfonamides.<sup>11, 12</sup> Penicillin diffuses from the blood stream into the pleural cavity and can be found in pleural fluids in concentrations which are somewhat lower than those of the blood. On the other hand, penicillin injected directly into the pleural cavity diffuses out into the blood stream rather slowly, and appreciable amounts are present in the pleural fluid for 24 to 72 hours after such an injection depending upon the dosage used, the size of the cavity and the thickness of its wall.<sup>13, 14</sup> Unlike sulfonamides,

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

With the technical assistance of Clare Wilcox.

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penicillin is not inhibited by pus, tissue autolysates or para-aminobenzoic acid,<sup>15</sup> but the penicillin activity may be destroyed by certain microorganisms or their products.<sup>16, 17</sup> Since the treatment of empyema must be continued for relatively long periods, the possible toxic effects of the therapeutic agents used are highly important. In this respect, too, penicillin, which is relatively free of toxic effects in man, is far superior to the sulfonamide drugs.

When all of these properties of penicillin are considered, it is not surprising that this agent should be selected as deserving of an intensive clinical trial in the treatment of empyema. A series of 24 cases treated with penicillin at the Boston City Hospital is presented in this paper together with an analysis of the important features of 237 additional cases collected from the literature.

#### PATIENTS TREATED AT THE BOSTON CITY HOSPITAL

The patients included in this report were admitted to the hospital between March 1944 and September 1945. All had infected pleural exudate demonstrated either at time of entry or some time later and were treated with penicillin for the empyema. Only four of them were admitted directly to the surgical services. The others were treated first on the medical wards and were transferred to surgery only if it was decided to operate. Patients in whom penicillin was first used at the time of operation or later are excluded.

Certain points should be kept in mind in interpreting the course and results in the present cases. The majority of these patients were treated during a period when penicillin was still scarce and its potentialities were only being explored. Until some of these potentialities were actually demonstrated, the decisions to resort to open thoracotomy were based largely on traditional indications. The length of the period of observation under the medical regime before arriving at this decision depended largely upon the willingness of the physicians and surgeons concerned to expose their patients to the risks which they supposed such a delay to entail. Owing to the variety of circumstances presented in the different patients, the treatment varied from case to case and could not be carried out according to any prearranged plan. An attempt was made in most instances to observe the effect of penicillin therapy as long as conditions warranted.

*Method of Study.* As soon as the presence of empyema was suspected (from the failure of a pneumonia to improve under prolonged and adequate therapy or from the physical signs and roentgenogram of the chest, persistent leukocytosis, etc.) a thoracentesis was performed. If purulent fluid was obtained and the patient was acutely ill at the time, treatment with penicillin intrapleurally, intramuscularly or by both routes was begun immediately. In most cases, however, the intrapleural therapy was withheld until after the presence of bacteria in the fluid was confirmed by culture or from stained smears. In a few of the patients, penicillin by the intra-

muscular route was postponed until 24 to 72 hours after the intrapleural injections were begun, and serial samples of blood were obtained during this interval in order to determine the serum concentrations obtainable by the use of the latter route alone. In other patients intramuscular penicillin therapy was started before the intrapleural injections or without the latter so that the penicillin levels in the pleural fluid resulting from the systemic therapy could be determined. Further chest taps were usually done every 12 to 24 hours at first and then at longer intervals for the purpose of measuring the concentration of penicillin still present in the fluid and for additional penicillin instillations. The results of the study of penicillin levels in the serum and pleural fluids have been reported elsewhere.<sup>14</sup> The serial dilution method of Rammelkamp<sup>18</sup> was used for these determinations. The sensitivity of many of the organisms obtained from cultures of the fluids were tested by the method of Rammelkamp and Maxon.<sup>19</sup> In addition to the cultures, smears and penicillin levels, each pleural fluid was usually studied also for its total protein and cell content. Its general character and the volume withdrawn were noted. Cultures of the blood and sputum were made in most of the cases before penicillin therapy was started.

As already noted, no uniform indications were used in deciding whether or when operation should be done. In general, rib resection was carried out when cultures of the pleural fluid remained positive after treatment, when fluid continued to form in large amounts or when there was evidence of loculation of inaccessible pockets. The cases of putrid empyema were all operated on although, in retrospect, it seems likely that some of them as well as several of the others might have been cured by continued conservative therapy without resort to operation.

Some of the pertinent data in each of the 24 cases are summarized in table 1. The course of the clinical and laboratory findings in seven of the cases illustrating a variety of responses is shown in figures 2 to 8.

*Age and Sex.* The age of the patients ranged from 4 to 72 years. Three-fourths of them were 40 or older and one-third were 60 or over. All but four were males.

*Pathogenesis.* The empyema followed a primary pneumonia in 15 of the cases, a pneumococcus being the causative agent in 14 whereas one case followed what was probably a primary staphylococcal pneumonia. Two cases occurred as complications of post-operative pneumonia following operations on the upper abdomen and a third occurred after a direct blow on the chest which resulted in atelectasis and probably pneumonia of the underlying lung. In Case 4 the empyema was part of a general picture of sepsis, the patient having had a mastoidectomy which was followed, in turn, by lateral sinus thrombosis and pneumonia. Case 10 was that of a chronic empyema of 20 years' standing in which many unsuccessful operations had been performed in an attempt to obliterate the cavity. The remaining four patients had putrid empyema of uncertain pathogenesis, but associated with pulmonary suppuration.



TABLE I  
Relevant Data in 24 Cases of Empyema Treated with Penicillin at Boston City Hospital to September 1945

No.	Sex	Age Years	Patho- genesis	Duration of Illness before Entry <sup>a</sup>	Days from Entry to First Tap	Bacteriology of the Empyema Fluid	Penicillin Therapy						Sulfonamides		Rib Resec- tion	Days in Hospital	Result
							Intramuscular		Intrapleural			Sulfa-	Days <sup>i</sup>				
							Total Units	Days <sup>i</sup>	Doses	Units Each	Doses to First Sterile Culture						
1	F	53	Pneumonia	4 days	12	Pneumococcus, type 1	635,000	3	3	33,000	2	merazine	(18)	Yes	60	Cured	
2	M	45	Pneumonia	7 days	<1	Pneumococcus, type 7	250,000	4	4	10,000	Not steril- ized	diazine <sup>e</sup>	8	Yes	139	Cured	
3	M	15	Pneumonia	3 days	4	Pneumococcus, type 1	785,000	7	4	25,000	2	diazine	7(12)	No	60	Cured	
4	F	20	Pneumonia after mas- toidectomy <sup>a</sup>	6 days	24	Streptococcus, alpha	2,980,000	17(8)	1 1	40,000; 50,000	Not steril- ized	diazine	17(12)	Yes	53	Died 1 day after operation	
5	M	59	Pneumonia	5 days	34	Pneumococcus, type 32	0	—	3	50,000	2	diazine	(25)	Yes <sup>i</sup>	70	Cured	
6	M	66	Pneumonia	21 day	4	Pneumococcus, type 1	150,000	2	4	20,000	2	merazine	(6)	No	12	Died; inade- quate therapy; chronic alcohol- ism	
7	M	72	Pneumonia	3 weeks	7	Pneumococcus, type 28	1,170,000	10	6	50,000	1	diazine	6(4)	No	64	Cured	
8	M	39	Pneumonia, post-opera- tive <sup>b</sup>	0	30	Mixed <sup>d</sup>	1,640,000	11	3	40,000	Not steril- ized	diazine	29(9)	Yes	188	Died after 2 op- erations; cavity not obliterated.	
9	M	23	Pneumonia	4 days	4	<i>Staphylococcus aureus</i>	1,735,000	14	1	40,000	1	diazine	6(5)	No	45	Cured	
10	M	39	Chronic em- pyema, 20 years; many operations	20 years	<1	<i>Streptococcus beta</i> ; <i>Staphylo- coccus aureus</i>	0	—	14	30,000	<i>Staphylo- coccus per- sistens</i>	0	—	No	20	Remained chronic	
11	M	50	Pneumonia	3 weeks	1	Pneumococcus, type 1	1,555,000	14(1)	8 <sup>e</sup>	50,000	6	diazine	7(7)	Yes	59	Cured	
12	M	42	Pneumonia	1 week	5	Pneumococcus, type 1	2,460,000	15(3)	13	50,000	1	diazine	(5)	No	59	Cured	
13	M	61	Pneumonia, post-opera- tive <sup>c</sup>	0	86	Pneumococcus, type 10A <i>Staphylococcus aureus</i>	1,390,000	15(16)	3	50,000	Not steril- ized	diazine	31(39)	Yes	178	Cured	

TABLE I—Continued

TABLE 1.—Continued

No.	Sex	Age Years	Patho- genesis	Duration of Illness before Entry <sup>a</sup>	Days from Entry to First Tap	Bacteriology of the Empyema Fluid	Penicillin Therapy						Sulfonamides		Rib Resec- tion	Days in Hospital	Result
							Intramuscular		Intrapleural				Sulfa-	Days <sup>d</sup>			
							Total Units	Days <sup>c</sup>	Doses	Units Each	Doses to First Sterile Culture						
14	M	44	Pneumonia	3 days	2	Pneumococcus, type 1	2,970,000	17	5	50,000	1	diazine	(4)	No	28	Cured	
15	M	60	Lung ab- scess (?); putrid	2 months	3	Streptococcus, alpha; para in- fluenza bacillus	1,770,000	15	3	50,000	Not steril- ized	diazine	18(3)	Yes	30	Broncho-pleural fistula; still draining (6 months)	
16	M	47	Chest trauma	1 day	6	Streptococcus, alpha	1,710,000	16	2	50,000	Not steril- ized	diazine	(12)	Yes	67	Cured	
17	F	4	Pneumonia	? 1 week	3	Pneumococcus, type 1	735,000	19	8	20,000	No cul- tures	diazine	(9)	Yes	87	Cured	
18	M	53	Pneumonia	3 weeks	2	Pneumococcus, type 11	1,290,000	10	6	40,000	No cul- tures	0	—	No	11	Died; comatose throughout	
19	F	66	Pneumonia	3 weeks	7	Pneumococcus, type 19	2,500,000	16(5)	6	50,000	1	diazine	(1)	No	27	Cured	
20	M	62	Pneumonia	1 month	<1	Pneumococcus, type 1	2,250,000	20	7	50,000	2	0	—	Yes	57	Cured	
21	M	40	Lung ab- scess (?); putrid	5 weeks	<1	Anaerobic streptococcus	3,320,000	14	4 2	100,000; 200,000	1	diazine	6	Yes	52	Cavity healing satisfactorily	
22	M	64	Broncho- pleural fis- tula; putrid	6 weeks	<1	Microaerophilic streptococcus; fusiform bacillus	4,160,000	26	4 5	100,000; 200,000	Not steril- ized	diazine	19	Yes	38	Cavity closing satisfactorily	
23	M	65	Pneumonia	2 weeks	12	Pneumococcus, type 32	440,000	3	5	50,000	Not steril- ized	diazine	67	Yes	115	Cured	
24	M	58	Metastatic carcinoma; putrid	0	47	Microaerophilic streptococcus	4,460,000	28	5 1	100,000 50,000	No cul- tures	diazine	15(21)	Yes	95	Cavity closing satisfactorily	

Abbreviations: Sex: M = Male; F = Female.

<sup>a</sup> Also had lateral sinus thrombosis. <sup>b</sup> Operated upon for perforated gastric ulcer. <sup>c</sup> After cholecystectomy. <sup>d</sup> *Staphylococcus albus*, alpha streptococcus, hemolytic *Staphylococcus aureus* and microaerophilic streptococcus. <sup>e</sup> Also 24 installations of 2,000 units each post-operative. <sup>f</sup> Cavity found obliterated, pleura 1 cm. thick and no free fluid. <sup>g</sup> Given only after the course of penicillin. <sup>h</sup> In this column duration is counted from onset of pneumonia or pleuritis. In Case 8, illness began 4 days after operation; in Case 13, it began on the fifteenth hospital day and in Case 24, the empyema developed while the patient was awaiting operation for rectal carcinoma. <sup>i</sup> Number of days before first thoracentesis is shown in parentheses; other numbers represent days after first tap.

## SERUM PENICILLIN LEVELS AFTER INTRAPLEURAL INSTILLATION

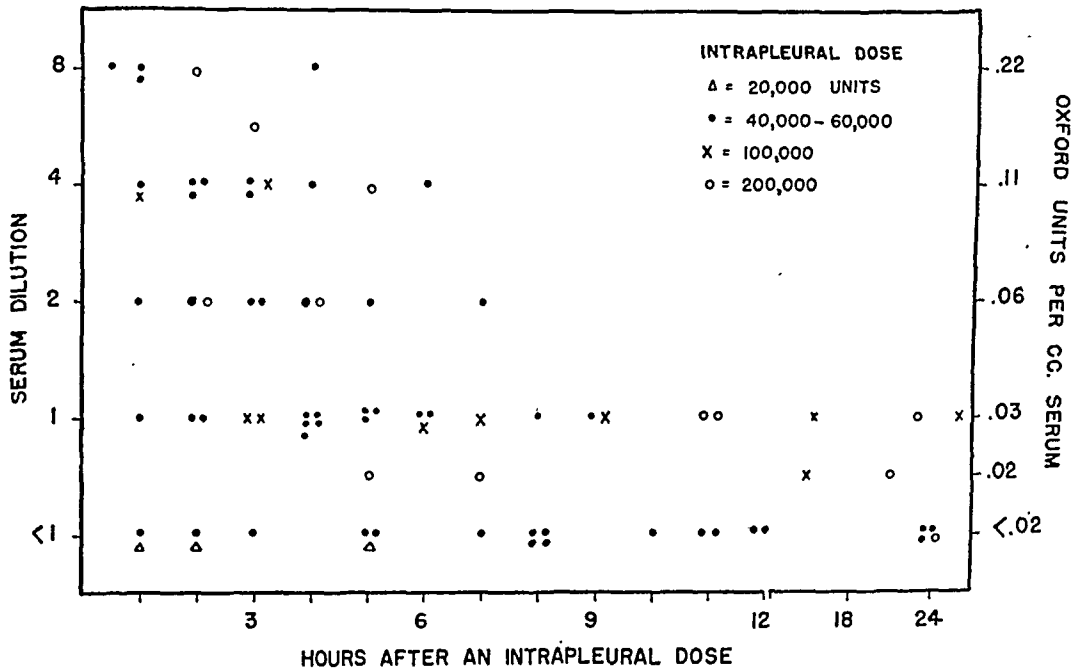


FIG. 1. Note. The vertical scale on the left gives the reciprocal of the greatest dilution of 0.2 c.c. of serum which, when added to 0.5 c.c. of a culture of streptococcus 98 containing about 10,000 streptococci, sterilizes the culture in 18 hours. The equivalent in units of penicillin is shown on the right.

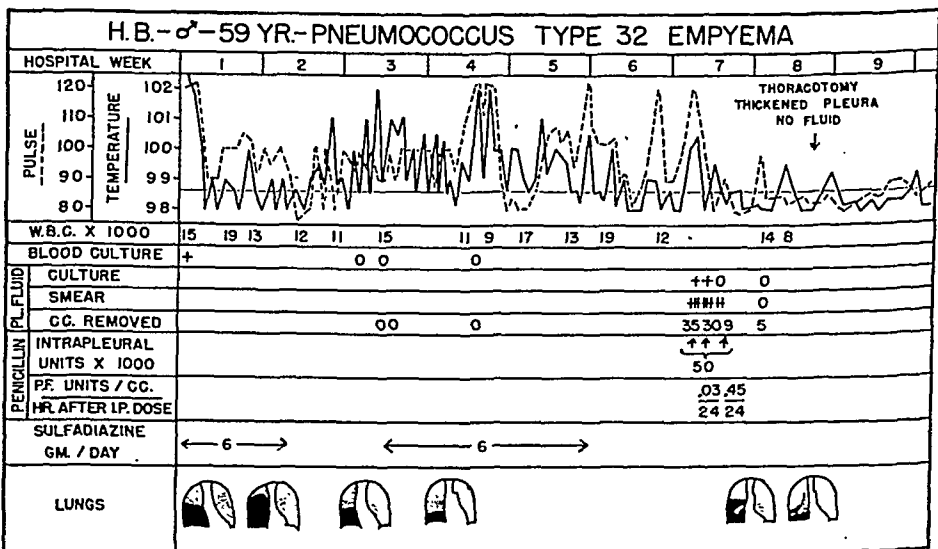


FIG. 2. Case 5. The patient had symptoms of pneumonia for five days before admission. He showed a satisfactory clinical response to the sulfonamides which were started on entry and discontinued on the ninth hospital day. Three days later he developed an irregular fever and leukocytosis which persisted in spite of a second course of sulfadiazine given over a period of 16 days. Three attempts at thoracentesis were unsuccessful but a small amount of thick pus was obtained on the forty-fifth hospital day. The patient improved markedly and the fever subsided after three intrapleural instillations of penicillin. Subsequent attempts to aspirate fluid were again unsuccessful. Because of persistent leukocytosis it was felt that the fluid had become loculated and a rib resection was done. The empyema cavity was found to be completely obliterated. There was no pus, but the pleura was 1 cm. thick. The wound healed rapidly.

**Bacteriology.** The pneumococcus was the most common causative organism and was found alone in 14 cases. In Case 13 a pneumococcus and a staphylococcus were found at various times, either separately or together, in the blood, in the pleural fluid and in peritoneal exudate. The pneumococcus was type 1 in eight cases, type 32 in two cases and of different types in each of the rest. In Case 12 the type 1 pneumococcus was identified by the Neufeld method in a fresh smear of the pleural fluid. It could not be grown in the cultures of the pleural fluid although it had been obtained in cultures of the sputum and blood of that case. Alpha hemolytic streptococci were obtained in two cases; anaerobic streptococci, microaerophilic streptococci and *Staphylococcus aureus* were each obtained in one case and the remaining four had mixed infections with streptococci and other organisms.

**Previous Therapy.** All of the patients except three received sulfonamides, usually before the penicillin was started. In addition, four of the patients had also been given intramuscular penicillin for three days or more before the presence of empyema was established by thoracentesis. There was no curative effect from the sulfonamides in these cases. In fact, the empyema developed while most of them were receiving sulfonamide drugs. The empyema was probably present before the penicillin was started in every

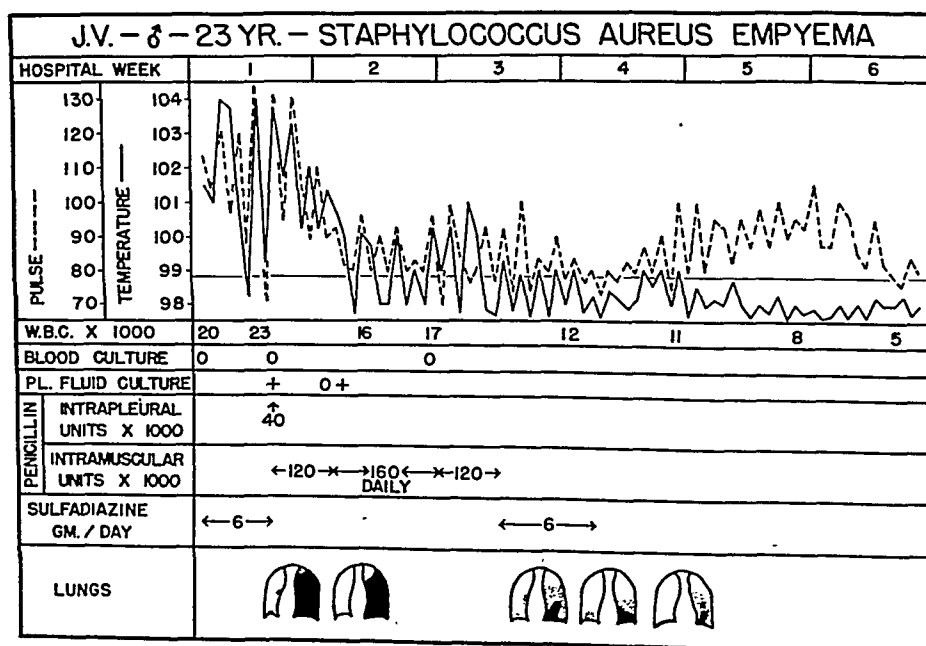


FIG. 3. Case 9. The patient had been ill at home for four days with fever and chest pain and had been inadequately treated with sulfonamides. In the hospital he was given sulfadiazine for five days without affecting the fever. On the fifth day, a thoracentesis yielded 200 c.c. of thin purulent fluid from which hemolytic *Staphylococcus aureus* was cultured. A second tap three days later produced only 2 c.c. of similar fluid which showed no growth on culture. A small amount of fluid was obtained on the following day and a culture of that fluid on broth showed no growth, but one made on blood agar yielded a few colonies of hemolytic *Staphylococcus aureus*. Only one intrapleural injection of penicillin was given but the patient received intramuscular therapy for 14 days and recovered completely without resort to operation.

instance although this cannot be stated with certainty in one or two of the cases.

*Penicillin Dosage.* Intramuscular penicillin was used in the treatment of 22 of the patients and was given for an average of about 15 days. It was given for seven days or less in five, for 10 to 21 days in 14 and for more than three weeks in the remaining three cases. The average intramuscular dose was about 120,000 units daily, four patients receiving 75,000 units or less, six receiving 150,000 units or more and the rest being given between 100,000 and 150,000 units daily.

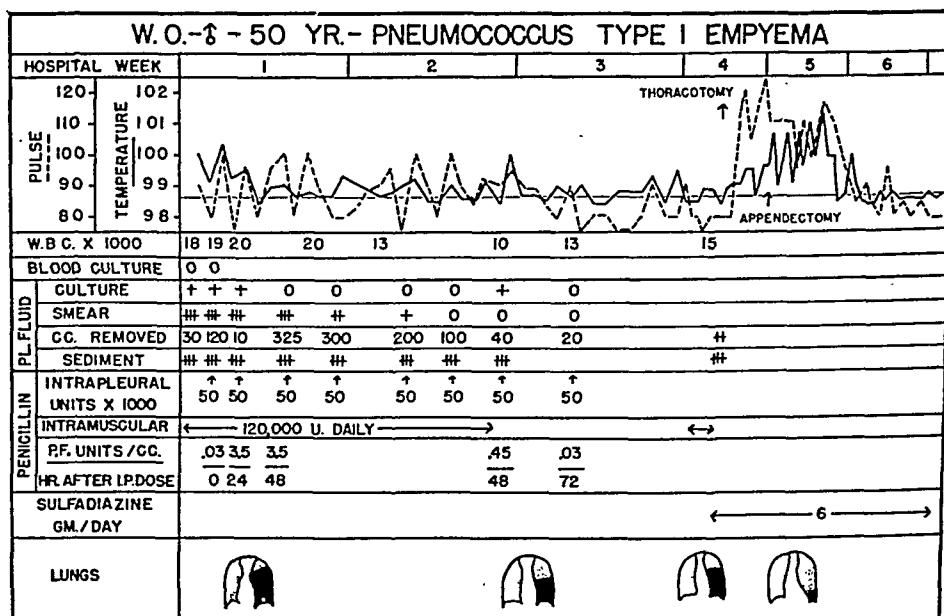


FIG. 4. Case 11. The patient had pneumonia at home for three weeks and was treated with sulfonamides. One week before admission, after apparently recovering from the pneumonia, he developed pleuritic pain, drenching sweats and fever. Pleural fluid cultures became negative after the second instillation of penicillin but organisms were seen in the smears of three subsequent specimens of fluid. After the sixth instillation, pneumococci were obtained on culture but could not be seen in the smear of the fluid. Although a subsequent tap again yielded sterile fluid, a rib resection was done and a large amount of purulent fluid was evacuated. The patient developed appendicitis four days later and an appendectomy was done. Recovery thereafter was uneventful. The cavity was completely obliterated and the wound healed four months after the rib resection.

Intrapleural penicillin was given in a volume of saline equal to about one-third of that of the pleural fluid withdrawn. The intrapleural dose varied from 5,000 to 200,000 units. Only four received 20,000 units or less, three received 100,000 or 200,000 units and almost all of the rest were given 40,000 or 50,000 units each time. The total number of intrapleural instillations in each case varied from 1 to 14 (average 6), eight of the patients received only one, two or three instillations. These are all exclusive of the intrapleural instillations given after the rib resections. There were no untoward reactions from any of the local injections.

*Sensitivity of the Organisms.* Tests for sensitivity of the organisms obtained from cultures of the pleural fluid were done on 12 strains from 11 cases and all were found to be quite sensitive. One strain of alpha hemolytic streptococcus from Case 8 was equal in sensitivity to that of a control streptococcus, No. 98 obtained from Dr. C. S. Keefer and required 0.008 unit to sterilize 1 c.c. of culture inoculated with approximately 10,000 streptococci, in 18 hours. The strains of pneumococcus from Cases 1, 5, 17 and 19 and the microaerophilic streptococcus from Case 8 required twice this concentration, whereas the strains of pneumococcus from Cases 7, 11

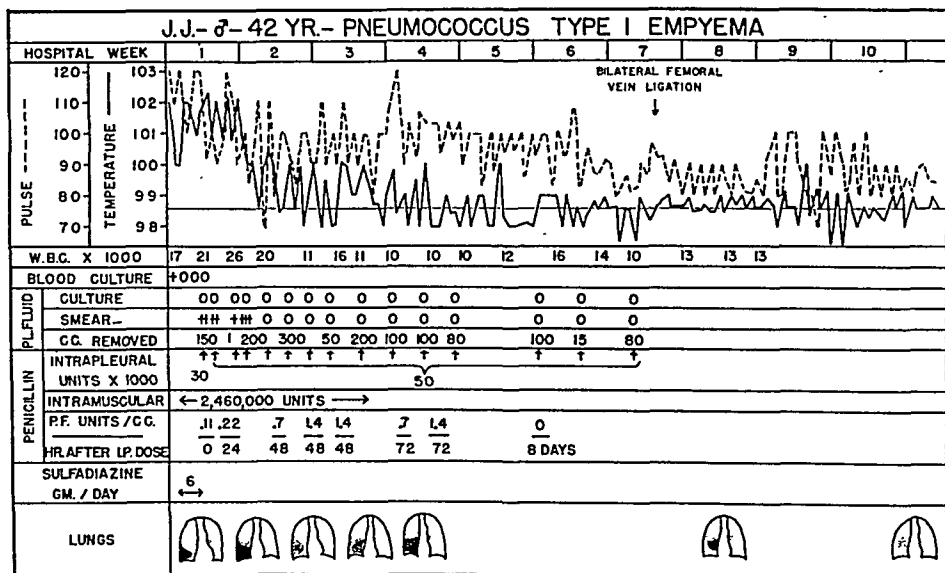


FIG. 5. Case 12. The patient was a chronic alcoholic who entered after about a week of illness during which he had chills, fever, pleuritic pain, dyspnea, cough and rusty sputum. He had frank delirium tremens during the first three days in the hospital and subsequently developed peripheral neuritis and thrombophlebitis. The latter was treated with bilateral femoral vein ligation. The first thoracentesis yielded thin purulent fluid, but subsequent ones produced thick pus. Organisms were seen in the first four specimens of pleural fluid. These could be easily identified by the Neufeld method as type 1 pneumococci in the first specimen, but they were irregular in shape and stained poorly in subsequent specimens. Cultures of all of the fluids were negative. The empyema was cured after 15 intrapleural injections of penicillin given over a period of six weeks. Intramuscular penicillin was also given for three days before and 15 days after the first tap. Operation was not done. Roentgenograms of the chest showed a progressive thinning of the pleura. The patient has subsequently had several admissions to the hospital for delirium tremens, but he has had no pleural or pulmonary symptoms.

and 14, the alpha streptococcus from Case 4 and the staphylococcus in Case 9 all required four times this concentration (that is, approximately 0.03 unit per cubic centimeter of culture) to accomplish a similar result.

*Penicillin Levels in Serum and in Pleural Fluids.* The findings of a number of workers who showed that penicillin given intramuscularly gets into the pleural cavity and that intrapleurally injected penicillin diffuses into the blood stream have been adequately confirmed in the present cases. The data have been presented, in large part, elsewhere<sup>14</sup> and the results may be summarized here briefly.

After a single intramuscular injection of 40,000 units, or during therapy with 15,000 or 20,000 units given by this route every two or three hours, the levels of penicillin in empyema fluid taken one to two and one-half hours after an injection ranged from 0.03 to 0.22 unit per c.c. These levels were obtained without intrapleural injections. The corresponding concentrations in the serum were usually from two to eight times as high. Considerably higher concentrations, up to 40 units per c.c., were found in the pleural fluid 24 hours after the local instillation of 30,000 to 60,000 units, and significant

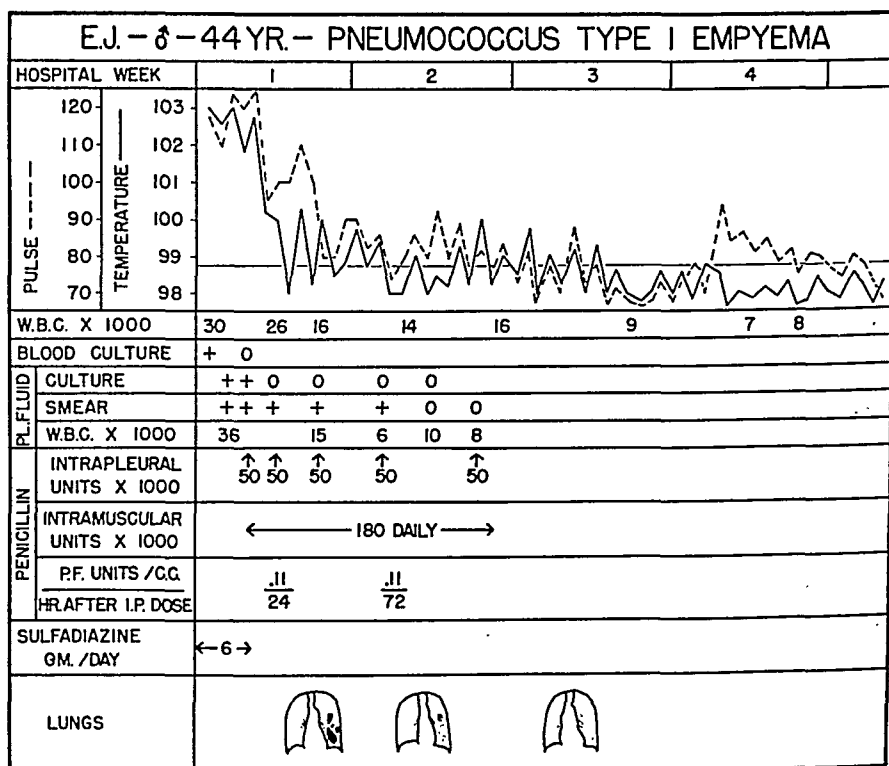


FIG. 6. Case 14. This patient's illness began with chills, fever, chest pain, cough and headache three days before he entered the hospital. He had received adequate doses of sulfonamides, but the blood culture taken at the time of admission was positive. Moderately thick purulent fluid was obtained by thoracentesis on the third hospital day, but the subsequent taps yielded progressively thinner fluid which decreased in amount from 200 to 20 c.c. Organisms were seen in the specimens obtained after the first three intrapleural instillations of penicillin, but they could not be grown in cultures of any of the fluids obtained after the first injection. Penicillin was also given intramuscularly and cure was complete without operation. Follow-up roentgenograms of the chest one and three months later showed no significant residual thickening of the pleura.

concentrations were found in some cases as long as 72 hours after these amounts were instilled even when systemic therapy was not given. After intrapleural injections of larger amounts still higher concentrations were found and these persisted for longer periods.

The levels in the serum after intrapleural injections of various amounts of penicillin during periods when systemic therapy was not being used are shown in figure 1. Concentrations similar to those obtainable after the

usual intramuscular doses and sufficient to be effective against the strains that were tested were maintained after intrapleural doses of 100,000 or 200,000 units for 24 hours or longer. Small doses gave lower levels and for shorter periods. With doses of 20,000 units, and sometimes with amounts up to 60,000 units, significant amounts were not found in the serum even during the first few hours.

*Effect of Penicillin on the Clinical Course.* Most of the patients improved markedly within 24 hours after penicillin treatment was started.

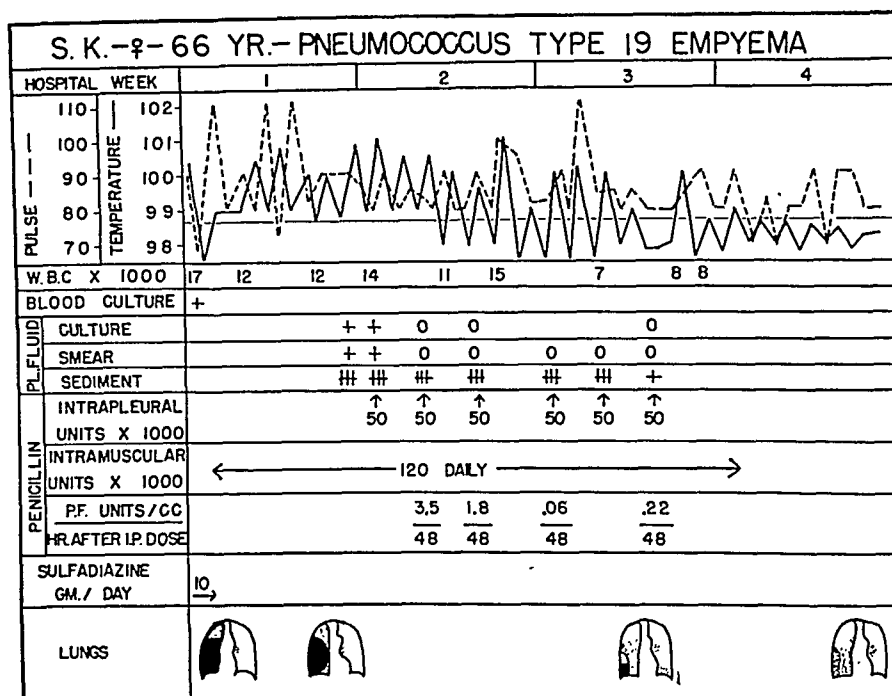


FIG. 7. Case 19. For three weeks before admission to the hospital this patient had a respiratory tract infection for which she was treated with sulfonamides, but her symptoms, which included cough, fever and pleuritic pain, persisted. Sulfadiazine was given after entry but this was discontinued after the first day because of nausea, vomiting, albuminuria, a rise in the blood nonprotein nitrogen to 61 mg. per 100 c.c. and failure of the respiratory symptoms to improve. Intramuscular penicillin was given thereafter. On the sixth hospital day a thoracentesis yielded 45 c.c. of thick greenish pus from which a pure culture of type 19 pneumococcus was grown. Six intrapleural injections of penicillin, 50,000 units each, were given over a period of 12 days. A cure was effected without operation. Roentgenograms of the chest taken after the last intrapleural instillation showed considerable pleural thickening, but this decreased progressively during the next two months.

This was true even when the intrapleural route alone was used. The rapid improvement was particularly notable in those who were acutely ill on admission and in those who eventually recovered completely without resort to operation. Many of the early beneficial effects may have been due to the withdrawal of pus from the pleural cavity. In those who were severely ill at the time, the temperature sometimes dropped to normal or nearly to normal, dyspnea decreased and the pulse became much slower. Sweating decreased and the appetite began to return rapidly in most cases. The leuko-



cyte count usually dropped more slowly and in some cases it remained elevated for several days. The improvement in the general condition was usually permanent rather than temporary as might be expected if the response were solely the result of the aspiration.

**Bacteriological Response.** Cultures of the pleural fluid became sterile and remained so after a single intrapleural dose in six cases, after two instillations in five cases and only after the sixth injection in one case. In none of the five patients who were given intramuscular penicillin for from 1 to 16

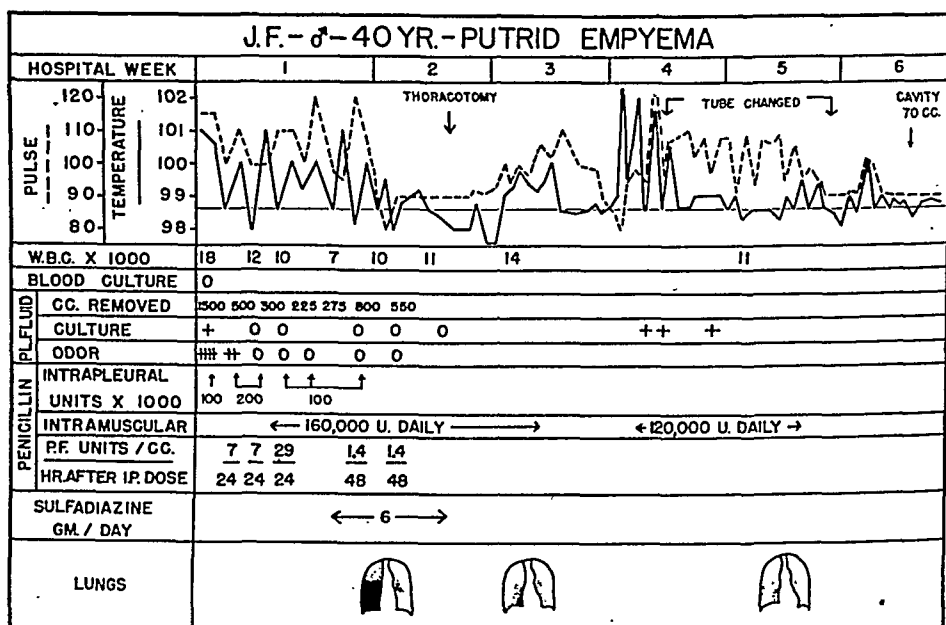


FIG. 8. Case 21. The patient had been treated at home for pneumonia for five weeks prior to admission to the hospital. His cough, fever and weakness persisted and he was very toxic, dyspneic and gravely ill on entry. There was marked improvement following the first thoracentesis and intrapleural penicillin instillation. The first fluid had an extremely foul odor but this was hardly perceptible in the second specimen obtained 18 hours later and subsequent ones were entirely odorless. An anaerobic streptococcus was grown with difficulty from the first fluid and cultures of later ones were sterile up to the time of operation. After the rib resection, however, cultures of the exudate have shown *B. pyocyaneus*, hemolytic *Staphylococcus aureus*, *B. coli* and alpha streptococci. Open thoracotomy was done because the fluid continued to form and could not be aspirated completely. The cavity is now almost completely obliterated 14 weeks after the operation.

days before the intrapleural therapy did the fluid become sterile before the first local injection. In Case 9 (figure 3) the culture of the last pleural fluid obtained by thoracentesis was still positive and the patient nevertheless recovered without rib resection. He had received only one intrapleural injection but was treated intramuscularly for two weeks thereafter. In three patients there was no adequate bacteriological follow-up and it is not known whether the fluid was sterilized as a result of therapy. Two of these three patients had rib resections and one died without operation. The latter was comatose on admission and failed to improve under treatment. In the remaining eight patients the cultures of the pleural fluid remained positive

throughout the period of observation. One of these patients received four intrapleural injections of 10,000 units each and two others each received two instillations of 50,000 units.

One observation of interest was the frequent persistence of organisms in the gram-stained smears for several days after the cultures had become sterile even with the addition of penicillinase. These organisms took the stain poorly, showed bizarre forms and varied considerably in size. The changes were similar to those described by Gardner<sup>20</sup> in susceptible organisms which are exposed to penicillin.

Operations were done in four of the patients in spite of the fact that the pleural fluid cultures had become sterile. In one of them (Case 5, figure 2) the empyema cavity was found to be entirely obliterated at the time of operation. Another (Case 21, figure 8) had a putrid empyema and the fluid rapidly lost its foul odor, but large amounts of fluid continued to form and a considerable amount of pus was evacuated at operation. The other two cases were subjected to operation in order to evacuate pus which could not be removed by aspiration.

Positive blood cultures were obtained at the time of admission in seven cases. Type 1 pneumococcus was obtained in Cases 1, 2, 3, 12 and 14, type 32 pneumococcus in Case 5 and type 19 pneumococcus in Case 19. In none of these cases, however, were further positive cultures obtained from the blood after treatment with sulfonamides or with penicillin was started.

*Effect of Penicillin on the Character of the Pleural Fluid.* There was no uniformity in the changes observed in the pleural fluid during penicillin therapy. In the cases that showed a good response there was usually a progressive decrease in the volume of fluid that could be aspirated. The fluid became thinner with rapid diminution in the amount of cellular and other debris in some cases. In others it became thicker or varied from one aspiration to the next. The foul odor of the putrid empyemata disappeared rapidly. There was no change in the appearance of the cells in stained smears.

*End Results.* There were nine patients who were treated with penicillin and aspirations alone and six of them were cured (five had pneumococcal and one had staphylococcal empyema). Case 10 was one of chronic empyema which had been subjected to several operations during the previous 20 years. Local instillations of penicillin through a catheter inserted into the chronic sinus did not effect a cure.

Two patients in the unoperated group died and the cause of their death was not entirely clear. One was a 66-year old chronic alcoholic (Case 6) whose general condition deteriorated progressively after admission. He received four intrapleural injections of 20,000 units each and was given intramuscular penicillin only during the last two days. The other patient (Case 18) entered the hospital in very poor condition after three weeks of treatment for pneumonia. His physician reported that his blood nonprotein nitrogen had risen to 125 mg. per 100 c.c. prior to entry, but the values found

in the hospital were not over 50. He remained semicomatose and failed to show any improvement after intrapleural and intramuscular penicillin in seemingly adequate amounts.

Operative drainage through rib resection was carried out in the remaining 15 patients. In nine of them the empyema cavity has been entirely obliterated and the sinus has completely healed. Three other patients have been discharged from the hospital and their cavities were closing at a satisfactory rate at the time of this writing.\* One patient, Case 15, had a putrid empyema which has become chronic and he still has a bronchopleural fistula and draining sinus seven months after the operation.

There were two deaths in the operated group. In Case 4, the illness began with mastoiditis which was followed by lateral sinus thrombosis and bacteremia and finally pneumonia and empyema. This patient died in spite of mastoidectomy, sulfonamides, penicillin and finally rib resection. In Case 8, there was a mixed infection of the pleura complicating pneumonia which, in turn, followed an operation for perforated peptic ulcer. The patient had a long hospital course during which he was twice subjected to rib resection. He died six months after the onset of his illness and the empyema cavity was never obliterated.

*Putrid Empyemas.* All four of the putrid empyemas, Cases 15, 21, 22 and 24, are included among those subjected to rib resections. The first of these cases is the one that was left with a chronic bronchopleural fistula and the others are all healing at a satisfactory rate.\* These patients all received intrapleural penicillin before the operation. Three of them showed only slight and gradual improvement while the fourth (Case 2, figure 8) who was almost moribund on admission showed striking improvement within 24 hours after the first intrapleural injection. The foul odor of the empyema fluid disappeared promptly in these cases. A similar clearing of the foul odor has been noted in the sputum of cases of putrid lung abscess with or without empyema, after penicillin treatment is started.

*Duration of Hospitalization.* The hospital stay of the six unoperated patients who were cured varied between 27 and 64 days and averaged 47 days whereas that of the corresponding cases in the operated group varied between 38 and 178 days and averaged 86 days. A comparison of the number of days in the hospital in these two groups of cases does not seem to be entirely justified since the operated cases were first subjected to the medical regime. On the other hand, it must be borne in mind that (1) some of the delay prior to operation would have taken place in any event, (2) a considerable part of the hospital stay in those not subjected to operation was purely to observe the effects and (3) the operated cases were not cured at the time of discharge in the same sense as those who were not subjected to operation. An additional one to four months was required in most of the

\*The wounds in these three patients have healed completely since this paper was submitted.

TABLE II  
Use of Penicillin in the Treatment of Thoracic Empyema: Summary of Bacteriology and of End Results in Cases Collected from the Literature Prior to October 1945

Authors and References	Total Number of Cases	Bacteriological Findings							Putrid Empyema	End Results						
		Pneumococcus	Streptococcus				Staphylococcus	Mixed Infections		Others	Penicillin and Aspiration, No Operation		Penicillin, Aspirations and Thoracotomy			
			Beta Hemolytic	Alpha or Nonhemolytic	Microaerophilic	Anaerobic					Cured	Chronic	Died	Cured	Chronic	Died
Group I. Empyemata other than those following thoracic injuries or operations																
Keefer et al. <sup>21</sup>	13	2	2	—	—	9	—	—	—	11 <sup>a</sup>	1 <sup>a</sup>	—	—	—	—	
Lyons <sup>22</sup>	2	—	2	—	—	2	—	—	—	2 <sup>a</sup>	—	—	—	—	—	
Bennett and Parkes <sup>23</sup>	5	—	—	—	—	2	—	—	—	5	—	—	—	—	—	
Tillett et al. <sup>24</sup>	21	3	—	—	—	2	—	—	—	20 <sup>e</sup>	—	—	—	—	—	
Dawson and Hobby <sup>25</sup>	74	3	—	—	—	1	—	—	—	3	—	—	—	—	—	
Flynn <sup>26</sup>	1	—	—	—	—	1	—	—	—	1 <sup>a</sup>	—	—	—	—	—	
Butler et al. <sup>27</sup>	18	7	5	—	1	—	—	—	—	16	—	—	—	—	—	
Lockwood et al. <sup>28</sup>	35	34	—	—	—	—	—	—	—	20	—	—	—	—	—	
Stainsby et al. <sup>29</sup>	3	—	—	—	—	1	—	—	—	2	—	—	—	—	—	
Entin <sup>9</sup>	7	4	—	—	—	1	—	—	—	5	—	—	—	—	—	
Kent and Sager <sup>30</sup>	5	2	2	—	—	1	—	—	—	—	—	—	—	—	—	
Roberts et al. <sup>31</sup>	12	3	4	—	—	2	—	—	—	3	—	—	—	—	—	
Fox <sup>32</sup>	9	3	3	—	—	3	—	—	—	8	1	—	—	—	—	
Blades et al. <sup>33</sup>	24	5	11	—	—	2	—	—	—	3	—	—	—	—	—	
Collen <sup>34</sup>	1	1	—	—	—	6	—	—	—	—	—	—	—	—	—	
Spink and Hall <sup>35</sup>	10	1	1	2	—	—	—	—	—	8	—	—	—	—	—	
Kramer <sup>36</sup>	1	—	—	1	—	2	—	—	—	1	—	—	—	—	—	
Healy and Katz <sup>37</sup>	5	—	—	—	—	2	—	—	—	5	—	—	—	—	—	
Rudensky et al. <sup>38</sup>	6	—	—	3	—	2	—	—	—	6	—	—	—	—	—	
Hirshfeld et al. <sup>39</sup>	13	3	2	2	—	3	—	—	—	2	—	—	—	—	—	
Farquharson et al. <sup>40</sup>	27	6	14	—	—	1	—	—	—	6 <sup>p</sup>	—	—	—	—	—	
Kullman and Crellin <sup>41</sup>	4	—	4	—	—	—	—	—	—	15 <sup>i</sup>	—	—	—	—	—	
Poppe <sup>42</sup>	8	—	—	—	—	5	—	—	—	4	—	—	—	—	—	
Present report	24	14	—	2	1	1	—	—	—	6	1 <sup>m</sup>	—	—	—	—	
Totals—Group I	261	110	50	15	3	43	27	10	15	144	4	8	94	4	6	
Per cent	100	42.1	19.2	5.7	1.2	16.5	10.3	3.8		55.4	1.5	3.1	36.2	1.5	2.3	

Group I. Empyemata other than those following thoracic injuries or operations

TABLE II—Continued

Authors and References	Total Number of Cases	Bacteriological Findings								Putrid Empyema	End Results					
		Pneumococcus	Streptococcus			Staphylococcus	Mixed Infections	Others	Penicillin and Aspiration, No Operation			Penicillin, Aspirations and Thoracotomy				
			Beta Hemolytic	Alpha or Nonhemolytic	Microaerophilic				Anaerobic		Cured	Chronic	Died	Cured	Chronic	Died
Group II. Empyemata complicating thoracic injuries or operations																
D'Abreu et al. <sup>43</sup> Nicholson and Stevenson <sup>44</sup> White et al. <sup>45</sup> Collis et al. <sup>46</sup>	28 <sup>a</sup> 15 14 44	4 — 1 —	2 — — —	1 — — —	— — — —	— — — —	8 — — —	12 — 5 —	1 <sup>b</sup> 15 <sup>b</sup> 8 <sup>b</sup> 44 <sup>b</sup>		9 2 1	— — —	— — Re-sults not stated	17 13 3	2 — 6 <sup>c</sup>	— — 4
	27	—	1	—	—	—	8	5	13	2	—	—	25	—	—	
	128	5	3	1	—	—	16	22	81	14	—	—	58	8	4	

<sup>a</sup> Operation not mentioned. <sup>b</sup> No growth, or etiology not established or not mentioned. <sup>c</sup> 2 of these had residual tuberculous effusions after the empyema was cured. <sup>d</sup> Results not stated in 1 case. <sup>e</sup> Results not stated or undeterminable. <sup>f</sup> 3 had closed drainage. <sup>g</sup> 3 operations done to collapse the empyema cavity. <sup>h</sup> 1 *H. influenzae* and 1 not determined. <sup>i</sup> 2 cases received intramuscular penicillin only. <sup>j</sup> 4 closed drainage. <sup>k</sup> All had tubercle bacilli and staphylococcus. <sup>l</sup> Both had broncho-pleural fistula. <sup>m</sup> Chronic case of 20 years' standing. <sup>n</sup> Intrapleural penicillin alone in 12 cases. <sup>o</sup> Died, operation not mentioned. <sup>p</sup> Two died, one of hemoptysis from a lung abscess and the empyema cavity at autopsy was completely obliterated. A third patient had encapsulated fluid but refused operation.

operated cases before the cavity was completely closed and the wound entirely healed. During this period they were ambulatory out-patients, partially incapacitated and under continuous observation.

### CASES REPORTED IN THE LITERATURE

Some of the relevant data concerning the penicillin treated cases of empyema that have been reported by a number of authors up to October 1945 are listed in table 2. The cases have been divided into two main groups, the one consisting of empyemata which developed on the basis of antecedent pulmonary infection (Group I) and the other comprising those which followed trauma to the chest or operations on the lung (Group II).

The cases in Group II need be mentioned only briefly. There were 128 cases in this group. The traumatic cases were chiefly complications of war wounds of the chest and the others followed pneumonectomies, lobectomies or external drainage of pulmonary abscesses. All of them may be considered in a special class which is the primary concern of the surgeons, and they are included here only for the sake of completeness. The data in these cases are very scant and it is not possible in most instances to draw any conclusions from the information given, as to effects of penicillin. Most of the authors have felt that the systemic and topical use of penicillin in such cases has reduced the mortality and the incidence and severity of infections. In 14 of the 84 cases in which the results were stated, a cure was obtained by penicillin and aspirations alone and secondary operations were apparently avoided. The 261 cases in Group I (including the 24 from the Boston City Hospital which have been discussed above) will be analyzed in greater detail.

*End Results.* The results of the use of penicillin in cases of empyema as reported by different authors are shown in table 2. A summary of the results in the cases of Group I is shown in table 3. Complete cures without resort to open thoracotomy for drainage were obtained in 55.4 per cent of the 260 cases. Rib resections were performed in 40 per cent of the entire group and the others were treated by aspiration and penicillin, the latter being given intramuscularly, intrapleurally or by both routes. At least several of those cured without operation received only intramuscular injections of penicillin and none intrapleurally.<sup>40, 43</sup> The final results with respect to mortality and the per cent of cures or of cases that became chronic were essentially the same in the operated and unoperated cases.

As already pointed out, the operated and unoperated cases are not strictly comparable. Operations were usually performed because treatment with penicillin and aspiration alone was considered inadequate for cure as judged by the failure to sterilize the pleural fluid or by the re-accumulation or loculation of the fluid. A review of the separate reports, however, suggests that the willingness to give the non-operative treatment an adequate trial was of paramount importance in determining the proportion of cases subjected to operation. Thus, many of the workers reported cures in over 85 per cent

of their cases without operation<sup>21, 23, 24, 27, 32, 35, 37, 38, 41</sup> whereas several others operated on all or nearly all of their cases.<sup>30, 31, 33, 42</sup>

*Etiology.* The causative organisms identified in the reported cases are listed in table 2. Some of the reports dealt chiefly or exclusively with pneumococcal empyemata<sup>24, 28</sup> but most of them included cases of varied etiology. The most frequent organisms found were pneumococcus, beta hemolytic streptococcus and staphylococcus, in that order.

TABLE III  
Summary of End Results of Penicillin Treatment in 260 Cases\* of Empyema  
Which Did Not Follow Thoracic Trauma or Operations

Result	Number of Cases			Per Cent of All Cases	Per Cent of Operative Group
	B. C. H.	Literature	Total		
<i>No Operation</i>	9	147	156	60.0	100.
Cures	6	138	144	55.4	92.3
Chronic	1	3	4	1.5	2.6
Died	2	6	8	3.1	5.1
<i>Operation</i>	15	89	104	40.0	100.
Cures	12†	82	94	36.2	90.4
Chronic	1	3	4	1.5	3.8
Died	2	4	6	2.3	5.8
<i>All Cases</i>	24	236	260	100.	

\* One of the reported cases is excluded for lack of adequate information.

† Includes 1 case in which cavity had been obliterated before operation.

The end results are correlated with the bacteriological findings in table 4. The number of cases due to each of the various organisms was not very large. It is of interest, nevertheless, that the proportion of cases cured without operation was quite similar in each instance except in those with mixed infections,—about one-fifth of the latter and between one-half and two-thirds of each of the others. The greatest proportion of deaths and of cases which became chronic was also among those with mixed infections. This was to be expected since some of the organisms were not susceptible to penicillin and these cases were often associated with severe pulmonary abscesses or with infections below the diaphragm. The cases in which micro-aerophilic or anaerobic streptococci were found were few in number but all of them were subjected to operation. These operations may have been fully justified, but it is not unlikely that they were done on the basis of traditional indications and because the extent of the beneficial effects of penicillin could not be predicted in the individual cases.

*Penicillin Therapy.* Details concerning the use of penicillin were not given in many of the reported cases. From the data that are available there seemed to be no close correlation between the final result and the size of the individual intrapleural doses, their number or the frequency with which they

were given. In one report<sup>27</sup> cures without operation were obtained in 16 out of 18 cases with initial instillations of from 10,000 to 40,000 units followed by 10,000 or 20,000 units in later ones. Others have used 50,000 to 100,000 units each time intrapleurally with a high incidence of apparent failures, that is, they still felt that operation should be done in those cases.

TABLE IV

Results of Penicillin Treatment in 248 Collected Cases of Empyema (Exclusive of Those Which Followed Thoracic Trauma or Operations) Arranged According to the Infecting Organisms

Organism	No Operation			Operation			Total	% Cures Without Operation
	Cures	Chronic	Died	Cures	Chronic	Died		
Pneumococcus	67	0	2	39	0	0	108	62.
Streptococcus:								
Beta hemolytic	25	0	0	21	0	2	48	52.
Alpha or Nonhemolytic	9	1	1	3	0	1	15	60.
Microaerophilic	0	0	0	2	0	1	3	
Anaerobic	0	0	0	2	0	1	3	
Staphylococcus	22	0	0	10	1	0	34†	65.
Mixed Infections	5	2	4	13	2	1	27	19.
Others*	5	0	0	4	1	0	10	50.
Total	133	3	7	94	4	6	248†	54.

\* No growth or organisms not identified.

† The result in 1 unoperated case was not stated.

The 24 cases from the Boston City Hospital are included, but 13 reported cases are excluded for lack of the necessary information.

The dose now most commonly used for each intrapleural injection is 50,000 to 100,000 units. In more than two-thirds of the cases the penicillin treatment was given over a period of three weeks or less and occasional cases were treated for as long as three to nine months.

The number of injections required to sterilize the pleural fluid was definitely stated in only 56 cases (table 5). In more than one-half of the cases, this was accomplished by one or two injections. Almost one-third of the cases, however, either required more than 10 injections before the fluid remained sterile or it was not sterilized before operation was done. Some authors merely stated that the fluid in the majority of their cases was steri-

TABLE V

Number of Intrapleural Injections of Penicillin Given before the Pleural Fluid Was Sterilized

Number of Injections	Number of Cases
1.....	20
2.....	9
3.....	3
4.....	3
5-10.....	3
More than 10.....	6
Not sterilized.....	12
Total.....	56



lized after one to three intrapleural injections<sup>21, 40</sup> while others merely noted that it was sterilized in most cases.<sup>33</sup> In a considerable number of cases thoracotomies were performed in spite of the fact that the fluid became sterile and remained so. In several instances organisms disappeared and positive cultures were again obtained later either while the penicillin was still being given or after it had been discontinued. In most of these cases thoracotomy was performed, but Tillett<sup>24</sup> re-treated or continued treating seven such cases and obtained cures in six of them without operation.

Many factors in addition to the number and size of the intrapleural penicillin doses play an important part in the sterilization and obliteration of empyema cavities. The susceptibility of the organisms to penicillin is obviously a prime factor. The duration of illness, the thickness of the pleura, the presence of thick pus, fibrin clots, loculations, bronchopleural fistulae or draining sinus may present serious mechanical difficulties.

With respect to intramuscular penicillin therapy the details have not been given by most authors. Some have merely stated that their patients received intramuscular penicillin in addition to the intrapleural injections. It was specifically mentioned as given in 43 cases and not given in 65 cases. It has been considered as particularly useful if the underlying pulmonary lesion is still active.<sup>28</sup> At least seven cases were cured by intramuscular penicillin alone.<sup>40, 43</sup>

*Sulfonamide Therapy.* It is also difficult to ascertain the exact number of patients who received sulfonamide drugs and the part they played in the outcome. They were probably used in the course of treatment in most of the cases, but it is definitely stated that they were given in only 53 of them. It is generally conceded that the sulfonamides have no curative effect once an empyema is established.<sup>28, 29, 37, 38</sup> Their effects, however, have been variously estimated. Lockwood, White and Murphy<sup>28</sup> noted that when sulfonamides were given prior to penicillin, the response to the latter was better. On the other hand, Burford and Blades<sup>47</sup> found that when sulfonamides were used for the primary infections of thoracic empyemata there was an increased occurrence of atypical empyema pockets which were often multiple, non-dependent, interlobar in location and offered unusual diagnostic and therapeutic problems.

*Irrigations.* Some authors advocated irrigation of the empyema cavity with saline before injecting penicillin so that the thinning of the exudate would facilitate aspiration and final clearing would be hastened.<sup>9, 24, 13</sup> Tillett, et al.<sup>24</sup> found the procedure advantageous in some cases but felt that the course was not significantly altered in others. Healy and Katz<sup>37</sup> considered the procedure worth while.

*Question of Chronicity and Residual Pulmonary Function.* The greatest objection to the non-surgical treatment of empyema has been the fear that the patient would be left with a thickened and perhaps immobile pleura and that pulmonary function would be reduced as a result. Unfortunately there have been no studies on pulmonary functions in the reported cases of

TABLE VI  
Relevant Data in 11 Penicillin-Treated Cases of Putrid Empyema Collected from the Literature to September 1945

No.	Authors and Reference	Authors' Case No.	Pathogenesis	Organisms in the Pleural Fluid	Treatment			Broncho-pleural Fistula	Results and Remarks
					Penicillin	Sulfa	Operation		
1	Dawson and Hobby	1	Not stated	Mixed infection	Intrapleural	—	None	—	Died.
2	Roberts et al.	12	Lung abscess	Anaerobic streptococcus; staphylococcus; gram-positive and gram-negative bacilli	Intrapleural; intramuscular	—	Rib resection	Yes	No response to penicillin alone; organisms sensitive in vitro.
3	Blades et al.	10	Lung abscess	Anaerobic streptococcus	Intrapleural and systemic	diazine	Thoracotomy	—	Pyopneumothorax, undrained for 3 weeks.
4	Rudensky et al.	4	Lung abscess	Nonhemolytic streptococcus	Intrapleural and intramuscular	diazine	None	Yes	Ambulatory 2 months after onset; cured.
5	Idem	5	Lung abscess	Streptococci; gram-positive and gram-negative bacilli	Intrapleural and intramuscular	diazine	None	Yes	Discharged from hospital in 2 months; cured.
6	Hirshfield et al.	3	Pneumonia	Alpha streptococci (no anaerobic cultures done)	Intrapleural	—	None	—	Operation refused; chronic encapsulated empyema with positive cultures.
7	Idem	6	Pneumonia after pelvic operation	Alpha streptococci; anaerobic streptococcus (nonhemolytic)	Intrapleural	—	Rib resection	Yes	Improved on penicillin; operation necessary to close bronchopleural fistula.
8	Idem	8	Lung abscess (post-tonsillectomy)	Anaerobic streptococci (hemolytic and nonhemolytic); unidentified bacilli and cocci	Intrapleural and intramuscular	—	None	—	Died after hemoptysis. Empyema found obliterated at autopsy; lung abscesses and consolidation.
9	Idem	9	Indefinite; massive effusion	Beta streptococci	Intrapleural	—	Rib resection	No	Not sterilized and cavity remained large; died of multiple pulmonary infarcts.
10	Idem	11	Not stated	No growth (aerobic); staphylococci and diphtheroid (smear)	Intrapleural	—	Rib resection	No	Developed abscess of chest wall, fluid lost foul odor, but did not decrease.
11	Idem	13	After intrapleural pneumolysis for tuberculous cavity	Anaerobic streptococcus; anaerobic coccus (unidentified); and diphtheroids	Intrapleural intravenous	—	Upper stage thoracoplasty	No	Fluid became odorless and decreased; cavity decreased only after operation.

See also Cases 15, 21, 22 and 23 in table 1.

penicillin-treated empyema. A number of observers, however, have reported observing a marked regression of pleural thickening in serial roentgenograms of the chest after treatment with penicillin and aspiration alone.<sup>3, 19, 24, 37, 40</sup> On the other hand, it has been pointed out that a sterile empyema is not necessarily a cured empyema<sup>3</sup> and also that some pleural thickening may be present without being apparent on roentgenogram.

The actual incidence of chronicity as well as the mortality was almost the same in both the operated and unoperated group, as already mentioned. It seems more pertinent to point out that impairment of function, pleural thickening and other difficulties are not necessarily less and may even be greater following operation than in the cases in which operation can be avoided. The operation usually leaves an ugly scar and often considerable deformity of the chest.

*Putrid Empyemata.* It has frequently been pointed out that putrid empyema is a special type which differs from other empyemata in its etiology, pathogenesis and prognosis.<sup>48-50</sup> In the majority of cases, it results from the rupture of a lung abscess so that the underlying pulmonary lesion must also be dealt with. Some of the important features of 11 penicillin-treated cases of putrid empyema collected from the literature are listed in table 6. These are in addition to the four cases included in the present report and listed as Cases 15, 21, 22 and 24 in table 1.

Five of the reported cases were not drained surgically, and of these two were cured. Interestingly enough, both of these patients had bronchopleural fistulae. A third patient refused operation and developed a chronic encapsulated empyema in which alpha hemolytic streptococci persisted. The other two patients died, one of them following a massive hemoptysis. At autopsy the empyema in the latter case was found to be completely obliterated, and the bleeding arose from an eroded blood vessel which traversed a pulmonary abscess cavity.

Surgical drainage was used after apparent failure to obtain a cure with penicillin and aspiration alone in six of the reported cases and in the four that were observed at the Boston City Hospital. One of the former died of multiple pulmonary infarcts and the final result in some of the others was not clearly stated. It was noted, however, that although the general condition of these patients improved strikingly and the foul odor of the fluid decreased rapidly, the results were much less striking in this group than in other types of empyema.

## DISCUSSION

In evaluating the cases reported in the literature it should be borne in mind that some of them were treated when the supply of penicillin was limited and it was of poorer quality than the products now available. The dosage used was often small and probably inadequate, and the intrapleural injections were frequently quite irritating. Much larger doses may now be

instilled into empyema cavities without any irritation. Many of the earlier cases were included as part of general clinical reports and lacked the details necessary for proper evaluation of the results. Still others resulted from war injuries or were reported from military establishments, and the patients were transferred to other hospitals or even to other countries so that adequate follow-up was impossible.

It is probably fair to say that at least some of the cases reported from surgical clinics did not receive an adequate trial on the conservative regime. It may also be said that in some of the cases in which operations seemed indicated and were carried out, the pre-operative penicillin therapy was inadequate and was not pursued with any great enthusiasm. This is equally true in some of the cases included in the present report and in some of those reported by others. Only after a considerable experience with conservative therapy has been accumulated and studied will it be possible to determine, with any reasonable assurance, the extent to which the traditional indications for operation in cases of empyema can be modified.

It is not surprising, therefore, that the proportion of cures without operation has varied widely in the different reports. Some authors have operated on practically every one of their cases and concluded that penicillin has altered the treatment of empyema only slightly or not at all.<sup>30, 33, 42</sup> Others obtained cures in almost all of their cases with penicillin and aspirations alone and maintain that the need for rib resection has been markedly reduced or is now rare.<sup>24, 32, 35, 37, 38, 41</sup>

On the basis of the accumulated experience at present it seems evident that more than one-half of all cases of empyema can be cured by repeated aspirations and local instillations of penicillin into the pleural cavity. Pneumococcal, beta hemolytic streptococcal and staphylococcal empyemata are more favorably affected than those due to anaerobic streptococci or to mixed infections. The associated pathologic lesions in the lungs and elsewhere may account for much of the differences and, in addition, the presence of organisms not susceptible to penicillin may account for some of the failures.

The effect of sulfonamide therapy on the incidence of empyema and on its course is difficult to assess. In the first place it must be considered that many patients with the severest forms of pneumonia who would otherwise have died have survived as a result of this form of therapy. It is in these cases, most of which have bacteremia and are treated late in the course of their disease, that the incidence of empyema is highest. In the milder cases and in those treated early, empyema is probably prevented by the proper use of sulfonamide. The final incidence of empyema among survivors, however, may not be appreciably less than before chemotherapy was used. Once frank empyema has developed, the sulfonamides have not been found to produce cures except occasionally when intensive treatment is given early in suitable cases.<sup>10</sup> On the other hand persistence in its use may raise difficulties as mentioned earlier.

Penicillin, when used in the treatment of pneumonia, may be expected to

produce a more favorable effect on the incidence of empyema. The data thus far available are too few to permit final conclusions as to the extent to which empyema will be prevented. In most of the cases in which empyema has followed penicillin-treated pneumonia, the possibility of inadequate therapy or of the empyema antedating the penicillin therapy cannot be excluded. It is more than likely that the early and adequate use of penicillin in pneumonia will materially reduce the incidence of empyema, in addition to curing a large proportion of those already present by the use of aspirations and intrapleural injections of the antibiotic.

The details of the treatment of empyema by aspiration and penicillin are still to be worked out. It seems reasonable to precede the intrapleural instillations of penicillin by irrigation with saline, especially where there is thick pus. This should facilitate the more complete removal of exudate and debris and permit better action of the penicillin. It has not been done consistently in the present series or in most of those reported by others. From the standpoint of the adequacy of the levels of penicillin in the pleural fluid, instillations at intervals of about 48 hours should be adequate provided that doses of 50,000 units or more are used. Early in the treatment, however, thorough aspiration of the pus seems highly important and should probably be done at 12 or 24 hour intervals until there is marked improvement.

The necessity for the systemic use of penicillin in addition to the intrapleural injections is not settled and will probably vary with the individual cases. It has usually been considered to be indicated in patients who still are acutely ill and toxic and still have underlying active pulmonary infection. The amounts of penicillin absorbed from the pleural cavity result in adequate bacteriostatic levels in the blood for 8 to 12 hours after an intrapleural dose of 50,000 units and for 24 hours or longer after doses of 100,000 or 200,000 units. The absorption is influenced by the size of the cavity, the thickness of its wall and probably other factors and therefore cannot always be predicted. The presence of bronchopleural fistula may also interfere with prolonged absorption so that intramuscular therapy might well be useful in this condition as in others where the patient is acutely ill.

The indications for rib resection and the optimum time when it should be done when penicillin treatment has been given remain to be worked out and will vary in different patients. The underlying pathology and the presence of mechanical factors which prevent adequate aspiration and local treatment will be important considerations. Loculation of fluid, excessively thick pus, fibrin clots, bronchopleural fistula, prolonged or chronic empyema, thick and rigid pleura, chronic draining sinuses and the persistence of organisms not susceptible to penicillin—all these are factors which interfere with the complete success of treatment with aspirations and penicillin alone and, in general, are likely to require surgical interference. It should be pointed out, however, that these factors alone do not necessarily prevent a cure by the conservative therapy. In many of the reported cures there was thick pus and fibrin clots. A number of cases with multiple empyema pockets<sup>9, 51</sup>

and even with bronchopleural fistula<sup>9, 24, 37</sup> have also been cured without surgical drainage.

In general, as long as the patient continues to improve, the cultures remain sterile and the fluid diminishes in quantity, it is safe to continue with conservative therapy. Most of the patients who eventually are cured improve markedly within the first two weeks. At the end of that period it should be possible to decide whether further conservative treatment is justified or whether operation should be undertaken. There seems to be no critical time after which it is unsafe to continue with the aspirations.

The dangers of chronicity, thickened pleura, impaired pulmonary function and other complications have already been mentioned. If empyemata are recognized early, the penicillin therapy can actually be started much sooner than it is usually safe to undertake open drainage. It is probably in this group of cases that the best results can be expected from the medical treatment. Even in cases in which the pleura is already thick, there are many reports of steady regression of the pleural thickening over a period of several months and the final results after non-surgical therapy were at least as satisfactory as in other cases following operation.<sup>9, 23, 24, 33, 40</sup> The periods of hospitalization and of disability, moreover, are definitely and considerably shortened if the operation can be avoided.

The effects of penicillin on the putrid empyemata were quite remarkable. It is no longer necessary to consider putrid empyema as an acute surgical emergency. With the local use of penicillin, supplemented in some cases with intramuscular injections, the condition of the patient may be improved markedly so that he is a much better operative risk and in a number of cases it may be possible to effect a cure without operation.

The treatment of the mixed infections of tuberculous empyemata has likewise undergone an important change as a result of the use of penicillin. Although the tuberculous infection persists, other organisms which are sensitive to penicillin can be eradicated. A thick purulent empyema may thus be converted to a serous tuberculous effusion with considerable improvement in the patient's condition.

It is not desired to leave the impression that rib resections and other forms of surgical drainage have been entirely replaced by penicillin therapy and simple aspirations. These operations will still be necessary in many cases. It is now possible, however, to cure a larger proportion of empyemata than ever before without resorting to open surgical drainage. Whenever this can be accomplished the patient will have a briefer illness and a shorter period of disability than if operation is employed.

#### SUMMARY AND CONCLUSIONS

The salient features of a series of 24 cases of empyema treated with aspiration and penicillin were presented and the results in similar cases

collected from the literature were analyzed. The penicillin in these cases was given intrapleurally, intramuscularly or by both of these routes.

Between 50 and 65 per cent of empyemata due to pneumococcus, hemolytic streptococcus and staphylococcus were completely cured without operative drainage. Among the cases of putrid empyema and of those with mixed infections non-operative cures were less frequent and more of them became chronic or died.

The general condition of patients with empyema improved markedly after treatment with penicillin and aspirations was started. Those with putrid empyema were probably much better operative risks as a result of preparation with this form of therapy.

In the favorable cases, sterilization of the empyema fluid was usually accomplished and the volume which could be aspirated diminished appreciably after three intrapleural instillations or less. The changes in the fluid following therapy, however, were not uniform and could not always be relied upon as a guide for further therapy or as an indication for operation. The foul odor of the putrid empyema cleared promptly after penicillin therapy was started.

In cases of empyema that were cured by aspirations and penicillin alone, the hospital course and convalescence were considerably shorter than in those who were subjected to operative drainage.

After intrapleural injection of penicillin in amounts of 50,000 units or more significant levels are maintained in the blood for several hours, the concentration and duration depending on the size of the dose and probably on the size and character of the empyema cavity. Systemic therapy is probably not essential in most cases, particularly if intrapleural injections of 100,000 units or more are given at 24 or 48 hour intervals.

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# QUINIDINE IN THE TREATMENT OF AURICULAR FIBRILLATION IN ASSOCIATION WITH CONGESTIVE FAILURE\*

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QUINIDINE ordinarily is considered contraindicated for auricular fibrillation in association with congestive failure, or, more accurately, in association with severe heart disease. In certain instances, however, its use has been life saving and has prolonged life for many months in a number of desperately sick patients (table 1). Positive criteria, therefore, are needed to know in which patients with serious heart disease the use of quinidine is justified. White<sup>1</sup> believes it is indicated in the presence of congestive failure if the ventricular rate cannot be controlled with digitalis. Levine<sup>2</sup> believes it is justified if the patient is doing poorly and it seems certain he will not become ambulatory. These are criteria that need emphasis and extension. One must ask in every case of auricular fibrillation and congestive failure whether quinidine should be given a trial. It is impossible correctly to predict in the individual case whether the patient will be benefited or harmed. Only a trial can determine this. The decision to use or not to use quinidine, therefore, must depend upon the relative danger of the disease and the drug. The real dangers of quinidine are those of embolism, sudden death, or production of ectopic ventricular rhythms. The dangers have been emphasized so much in connection with the use of the drug in congestive failure and severe heart damage that quinidine often is automatically excluded and never even considered in treatment.

This study concerns itself with a statistical evaluation of the dangers of quinidine, particularly in the presence of congestive failure and serious heart disease, in an attempt to establish positive criteria for treatment. The hazard of embolism, we believe, may be ignored for the reasons given below.

*Hazard of Embolism.* Embolism is apparently a greater hazard if auricular fibrillation is allowed to continue than if the rhythm is restored to normal. The risk of embolism is a constant one as long as the arrhythmia continues, whereas the risk of embolism from quinidine is confined to a period of a few days following return to normal rhythm. The latter hazard is much less than the former and is about 4 per cent.<sup>3</sup> The risk is about the same for the same period of time even if no quinidine is given.<sup>4</sup> Auricular fibrillation persisting over a long period of time produces embolism in a high percentage. Laws and Levine<sup>5</sup> found that 16 of 61 patients with rheumatic heart disease and auricular fibrillation died of embolism and throm-

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TABLE I  
Desperately Sick Patients with Auricular Fibrillation and Congestive Failure (or Repeated Emboli) Who Responded to Quinidine

No.	Author	Sex and Age	Etiology	Duration of Auricular Fibrillation	Degree of Congestive Failure	Reason for Quinidine	Results	Remarks
1	White and Blumgart <sup>19</sup>	F 49	Rheumatic mitral stenosis with aortic regurgitation. Active rheumatic infection.	Recent EKG "flutter and fibrillation"	Edema up to knees	Repeated pulmonary emboli. Hoped to avert further emboli by return to normal rhythm.	Normal rhythm returned, no further pulmonary infarction. Congestive failure subsided. For 5½ yrs. perfectly well.	Digitalis given for 12 days. "Chances for the patient slight before quinidine given"
2		M 19	Rheumatic mitral stenosis with aortic regurgitation. Active rheumatic infection.	Not stated	Liver enlarged 3 fingers below costal margin.	Digitalis in large amounts did not control ventricular rate of 150.	Normal rhythm third day ventricular rate 90. Within a few days congestive failure gone.	Life saved but arrhythmia became established 2 years later.
3	Sokolow, M. <sup>20</sup>	M 49	Uncertain	6 years	No edema or liver enlargement.	Repeated emboli to arm and both legs.	Normal rhythm second day. No more embolism.	Apparently return to normal rhythm prevented further emboli and prolonged life for 11 months.
4	Kohn and Levine <sup>21</sup>	M 64	Arteriosclerotic heart disease with hypertension, angina with nocturnal dyspnea—1½ years.	5 years	Cyanosis, dyspnea, edema, enlarged liver, enlarged heart. Cheyne-Stokes breathing.	Inadequate response to rest and digitalis.	"Almost miraculous response" 2½ years later normal rhythm. Practicing medicine.	Digitalis given until toxic symptoms with slight improvement.
5	Korns, H. M. <sup>22</sup>	M 52	Rheumatic mitral disease.	10 years pulse uneven	Edema, ascites, air hunger.	Incapacitated for 9 months with congestive failure.	"Rapidly restored" compensation. Able to return to work as streetcar conductor.	Rest and digitalis improved him, but a cardiac invalid with auricular fibrillation. With sinus rhythm was able to work.
6	Korns, H. M.	M 65	Uncertain	Not stated	Edema, orthopnea, extreme cardiac enlargement.	With digitalis alone was not ambulatory, orthopnea and precordial distress persisted.	Normal rhythm returned. Orthopnea left.	Returned a bed patient to an ambulant.

TABLE I—Continued

No.	Author	Sex and Age	Etiology	Duration of Auricular Fibrillation	Degree of Congestive Failure	Reason for Quinidine	Results	Remarks
7	Van Nuy, F. <sup>23</sup>	M 61	Not stated	Not stated	Dyspnea, edema, enlarged heart. Ventricular rate 160-190. Edema of legs, cyanosis.	Despite large doses of digitalis, congestive failure persisted. tachycardia persisted.	Returned to normal rhythm after 4.4 gm. Congestive failure relieved.	
8	Levy, R. L. <sup>21</sup>	F 32	Rheumatic mitral stenosis.	6 weeks	Hydrothorax, ascites 3300 c.c. removed from chest.	Not adequate response to rest and digitalis.	Returned to normal rhythm, congestive failure relieved. Seen 6 months after return to normal rhythm.	
9	Bertucci, J. <sup>23</sup>	F 69	Arteriosclerotic heart disease.	4 years	Dyspnea, cyanosis, edema, ventricular rate 180.	Despite vigorous treatment, became progressively worse.	Returned to normal rhythm, congestive failure relieved.	
10		F 68	Arteriosclerotic heart disease.	Not stated (Probably several years)	Dyspnea, edema, liver enlarged, ventricular rate 160.	Vigorous treatment but failed to respond. Death seemed inevitable.	Returned to normal rhythm. Congestive failure relieved.	
11		M 69	Arteriosclerotic heart disease.	5 years	Dyspnea, edema, ascites, ventricular rate 180.	No response to digitalis.	Returned to normal rhythm. Congestive failure relieved.	
12	Brill, I. C. <sup>23</sup>	F 43	Uncertain	3 months	Hydrothorax, ascites, edema.	Fairly recent auricular fibrillation.	Returned to sinus rhythm and has remained so until 1945.*	
13	Hay, J. <sup>27</sup>	F 50	Followed influenza	6 months	Edema, dyspnea, tachycardia.	Response to other treatment not adequate.	"Since return to normal rhythm 8 months ago, she has been back at work."	
14	Askey	M 41	Rheumatic mitral stenosis.	10 years	Orthopnea, enlarged liver.	Failure to respond to digitalis, rest, diuretics.	Returned to normal rhythm. Congestive failure gone.	Occasional attacks of paroxysmal auricular fibrillation.
15		M 60	Arteriosclerotic heart disease.	8 months	Cyanosis, orthopnea, anasarca.	Inadequate response to rest and digitalis.	Returned to normal rhythm. Has persisted 8 months. Congestive failure gone.	Is ambulatory, but restricted activity.

\* Personal communication from author.

bosis (26 per cent). Only one of 87 patients without auricular fibrillation died of embolism and thrombosis. Among 808 patients with varying types of heart disease and auricular fibrillation, Hall<sup>6</sup> reported 179 instances of embolism in 508 patients not receiving quinidine (35.2 per cent). In 123 (24.4 per cent) the emboli were clinically recognized. In 300 patients who received quinidine, only nine instances of embolism were observed (3 per cent). Of 257 patients with auricular fibrillation who died, Hall said 109 (42 per cent) had had one or more emboli, often several years before death. Evans<sup>7</sup> found that 10 of 39 patients with long standing auricular fibrillation averaging 10 years had had at least one episode of embolism during the period of observation (24 per cent). Carr<sup>8</sup> found that 16 patients of 100 with auricular fibrillation had had emboli at some time during the course of disease. If the above statistics apply generally, the risk of eventual embolism would seem to be about 4 per cent if quinidine is given for auricular fibrillation and approximately 15 to 20 per cent if the auricular fibrillation is allowed to persist. The fact that the risk with quinidine is confined to a period of a few days renders the causal relationship quite obvious, whereas the greater danger of allowing the auricular fibrillation to persist is obscured by the fact that sporadic embolism occurs over a longer period of time. It may then be regarded as the inevitable outcome of cardiac disease rather than the result of the persistent arrhythmia. A history of previous embolism thus is not necessarily a contraindication, but may actually be an indication for the use of quinidine as a preventive for further embolism by elimination of the arrhythmia. The views of several authors are perhaps expressed in that of Smith and Boland.<sup>9</sup> They said: "In this group the patients have considerable heart disease with varying amounts of heart failure, and emboli continued to form. These emboli may be cerebral, pulmonary, or may occur in the peripheral vessels. In this group of cases we believe that one is justified in taking a greater risk to establish normal rhythm. The patients are less likely to have emboli if normal rhythm can be restored." The danger of embolism from persistent auricular fibrillation is particularly evident if the arrhythmia is associated with myocardial infarction. In 84 patients observed at the Los Angeles County General Hospital, 55 had persistent auricular fibrillation, and 29 had only a transient arrhythmia. In only 11 per cent of the deaths in the latter group was embolism the cause of death, whereas in the group in whom the auricular fibrillation persisted, nearly one-third of the deaths were due to emboli.<sup>10</sup> In the absence of convincing statistical data to the contrary, we believe that the danger of embolism cannot be cited as a contraindication to the use of quinidine. The statement of White<sup>1</sup> seems sound. "Embolism can occur with persistent auricular fibrillation alone and in fact does so then as often as upon the return of the heart to normal rhythm."

*Sudden Death as a Hazard of Quinidine.* Sudden death is accepted as a danger of quinidine administration. The mechanism may vary. Death may result from respiratory paralysis, ventricular fibrillation, or cardiac

standstill from paralysis of both pace-makers in the sino-auricular and auriculoventricular nodes. Although ventricular fibrillation from quinidine may not always result in sudden death, such instances are rare and may be ignored statistically. Parkinson and Campbell<sup>3</sup> found that sudden death occurred in nearly 4 per cent of 554 patients with auricular fibrillation treated with quinidine. It occurred after large, moderate, or small doses and whether normal rhythm had been restored or not. Sudden death, however, is a natural risk in heart disease, and is not uncommon in patients with auricular fibrillation who have received no quinidine. Cookson<sup>11</sup> found it responsible for nine of 86 deaths in patients with auricular fibrillation receiving no quinidine (10.4 per cent). DeGraff<sup>12</sup> found it as a cause of death in about 2.5 per cent among 276 patients with auricular fibrillation and rheumatic heart disease. Bramwell and Ellis<sup>13</sup> report an instance of sudden death in a man, aged 25, with old standing rheumatic carditis, auricular fibrillation, and extreme dilatation of the left auricle while receiving small doses of digitalis. When using the bed pan he collapsed and died. Necropsy revealed no cause of death. Had his unexpected death followed the administration of quinidine, they said, one would have been tempted to attribute it to the use of that drug. The danger of sudden death if quinidine is used in certain conditions is known to be especially high. Quinidine can both initiate and prevent ventricular tachycardia and ventricular fibrillation. The danger of the former is chiefly if quinidine is given in the presence of conduction defects.<sup>14, 15</sup> Others believe it can occur if digitalis is not used with quinidine in the treatment of long standing auricular fibrillation.<sup>16</sup> The fear of sudden death is the main contraindication to the use of quinidine for auricular fibrillation if congestive failure is associated. If the natural risk of sudden death from the condition itself is greater than the risk from the drug, then quinidine is indicated. What is the risk of sudden death from quinidine in auricular fibrillation associated with congestive failure?

*Risk of Sudden Death from Quinidine in Relation to the Presence of Congestive Failure.* The reports in the literature of 839 patients with auricular fibrillation treated with quinidine who could be segregated into those with congestive failure, and those without congestive failure, were studied and the percentage of those with sudden death was determined. Cookson's<sup>11</sup> description of sudden death is good. "The patient may cry out, become pale and pulseless, perhaps give a few gasps, and is dead." If a necropsy is obtained, no cause of death is found. Sudden death occurred in 11 of 275 patients with congestive failure (4 per cent), and in 10 of 564 patients without congestive failure (1.8 per cent) (table 2). The surprising finding was the relatively small percentage of cases with sudden death in the group with congestive failure. The per cent of incidence was not as high as in Cookson's group of 84 patients without treatment, but was higher than the approximately 2.5 per cent in DeGraff's series of 276 patients.<sup>12</sup> A controlled study of the effect of quinidine is that of Berman and Blumen-

TABLE II  
Sudden Death Occurring in Patients with Auricular Fibrillation Treated with Quinidine (with and without Congestive Failure)

Authors	Pts. with Congestive Failure		Pts. without Congestive Failure		Comments
	No. of pts.	No. of sudden deaths	No. of pts.	No. of sudden deaths	
Viko, L. E., Marvin, H. M., and White, P. D.: Arch. Int. Med., 1923, xxxi, 345.	48	2	23	0	
Burwell, C. S., and Dienneide, F. R.: Arch. Int. Med., 1923, xxxi, 518.	13	1	3	0	
Bramwell, J. C., and Ellis, R.: Lancet, 1928, ii, 960.	7	0	20	0	
Kohn, C. M., and Levine, S. A.: Ann. Int. Med., 1935, viii, 923.	19	0	30	2	
Parkinson, J., and Campbell, M.: Quart. Jr. Med., 1929, xxii, 281.	18	2	46	0	
Parkinson, J., and Nichol, J. W.: Lancet, 1922, xi, 1267.	4	0	24	0	
Wolff, L., and White, P. D.: Arch. Int. Med., 1929, xliii, 653.	23	0	45	1	
Stroud, W. B., LaPlace, L. B., and Reisinger, J. A.: Am. Jr. Med. Sci. 1932, clxxxiii, 48.	0	0	66	2	
Newman, W. W., and Spiro, H.: Calif. and West. Med., 1932, xxxvii, 19.	0	0	66	1	
Hewlett, A. W., and Sweeney, J. P.: Jr. Am. Med. Assoc., 1921, lxxvii, 1793.	4	0	8	1	
Campbell, M., and Gordon, F. W.: Quart. Jr. Med., 1936, sns, 205.	0	0	91	0	
Clarke-Kennedy, A. E.: Quart. Jr. Med., 1922-23, xvi, 204.	11	0	33	1	
Smith, H. L., and Bolland, E. N.: Jr. Am. Med. Assoc., 1939, cxiii, 1017.	16	2	24	1	
Wolferth, C. C.: Am. Jr. Med. Sci., 1921, clxii, 812.	8	0	4	0	
Korns, H. M.: Arch. Int. Med., 1923, xxxi, 36.	10	0	3	0	
Hamburger, W. W.: Jr. Am. Med. Assoc., 1921, lxxvii, 1797.	6	0	2	0	
Jamieson, R. A.: Canad. Med. Assoc. Jr., 1925, N.S. xv, 782.	31	4	18	0	
Harris, K. E.: Heart, 1929, xiv, 283.	5	0	37	0	
Riecker, H. H.: Am. Jr. Med. Sci., 1925, clxx, 205.	52	0	0	0	
Smith, F. J., and Clarke, N. E.: Arch. Int. Med., 1925, xxxvi, 838.	0	0	20	1	
Total	275	11	564	10	
Hay, J.: Lancet, 1924, ii, 543.	Not Stated		Not Stated		Of 265 patients not classified as to presence or absence of congestive failure, 8 died sudden deaths.
Maynard, E. P.: Am. Jr. Med. Sci., 1928, clxxv, 55.	Not Stated	1	Not Stated	0	53 cases not segregated as to presence or absence of congestive failure.
Levy, R. L.: N. Y. State Med. Jr., 1922, xxii, 276.	Not Stated	1	Not Stated	0	25 cases not segregated.
Berman, R., and Blumenthal, J. S.: Minn. Med., 1942, xxv, 198.	Not Stated	2	Not Stated	3	In 97 patients, quinidine was given to alternate cases, not classified as to congestive failure.
Sappington, S. W.: Jr. Am. Med. Assoc., 1922, lxxviii, 59.	Not Stated	1	Not Stated	0	

thal<sup>17</sup> who gave quinidine to alternate patients with auricular fibrillation. Of the 48 treated patients, five died sudden deaths; of 49 untreated patients, two deaths occurred, but the type of death was not given. Of the five with sudden death, two had congestive failure. One must deduce that sudden death probably was a drug hazard in this series. The results of the study of these 839 patients suggest, therefore, that sudden death is apparently not a drug hazard of quinidine in patients without congestive failure, but is apparently a hazard in those with congestive failure, although statistically slight. If this is so, what are the criteria that decide when and where to use the drug in congestive failure?

*Patients with Congestive Failure Not Responding to Other Measures.* There can be little objection to the use of the drug in such instances as those described in the literature as hopelessly sick despite all other accepted measures. Such instances are illustrated in table 1. In these cases the etiology was rheumatic in four, and non-rheumatic in nine. In two instances, quinidine was given because of repeated emboli, in one because the ventricular rate could not be controlled by digitalis, and in the others, because the congestive failure was progressive despite digitalis and other appropriate measures. In addition, we wish to report two desperately sick patients with auricular fibrillation, congestive failure, and intraventricular block, ordinarily a contraindication for quinidine, in whom the drug restored normal rhythm and we believe prolonged their lives.

#### CASE REPORTS

*Case 1.* A male, aged 41, was admitted to St. Vincent's Hospital April 10, 1944. The patient was known to have had rheumatic heart disease for 15 to 20 years and auricular fibrillation for over 10 years. For several months he had been orthopneic and had developed liver enlargement and ascites. He had been in another hospital just prior to this admission where he had received digitalis, a salt free diet, and mercurial diuretics. On examination, he showed marked congestive failure with cyanosis, orthopnea, and an enlarged tender liver. For three weeks he was put on a régime of rest, digitalis, and mercurhydryn, 2 c.c. intravenously every three days, but he still continued in congestive failure with an enlarged tender liver and orthopnea. An electrocardiogram revealed auricular fibrillation with intraventricular block and premature ventricular contractions. At this time it was considered that the status of the patient was desperate and the condition hopeless. Despite the usual contraindications for quinidine, that is, long standing auricular fibrillation with congestive failure and conduction defects, it was decided to give quinidine. Another apparent contraindication was the fact that the ventricular rate was not fast; it was 80. He was given an initial dose of three grains at 12:00 noon. Six grains were given at 1:00 p.m., 3:00 p.m., 5:00 p.m., 7:00 p.m., and 9:00 p.m. Between 9:00 p.m. and 11:00 p.m. the heart became regular with a ventricular rate of 80. The next day the electrocardiogram showed normal sinus rhythm with prolongation of the PR interval and intraventricular block. The relief of the orthopnea was remarkable. Within a few days he was able to lie flat in bed without difficulty. The constant epigastric distress and pain due to the enlarged liver disappeared along with the liver enlargement, and five days later he insisted on going home because he felt so much better. Thereafter he had no return of congestive failure. Despite quinidine administration every four



hours night and day, it was impossible to prevent occasional intermittent bouts of transient paroxysmal auricular fibrillation. Despite these annoyances, however, he viewed with alarm the thought of any return to the persistent auricular fibrillation. In our opinion, this man's life was definitely prolonged by return to sinus rhythm. On January 22, 1946 he was ambulatory and comfortable.

*Case 2.* A male real estate dealer, aged 60, while hunting in December 1941, developed severe precordial pain without dyspnea, radiating into both arms. The pain lasted two to three days. Following that, he noticed dyspnea on walking uphill and easy fatigue. He continued working, but developed a cough, and the dyspnea became gradually worse. In December 1943, he developed edema of the ankles. He was given digitalis. He did no work between January and July 1944. He then irrigated some land, working with a shovel for six hours, and became much worse, developed orthopnea, and the edema of the ankles increased. For several weeks prior to his admission to the hospital on August 23, 1944, he had been receiving digitalis and mercurhydryn injections twice weekly, but the orthopnea and anasarca were not improved. Examination on admission revealed a patient with cyanosis, orthopnea, and massive edema of the legs to above the knees, and of the sacrum. The liver was enlarged six fingers' breadth below the costal margin. His vital capacity was 2 liters or 46 per cent of normal. The venous pressure on August 23, 1944, was 26 centimeters of water. The electrocardiogram revealed auricular fibrillation with premature ventricular contractions and intraventricular block. The risk of the condition in this patient was considered greater than the risk of the drug. He was given three grains of quinidine at 4:00 p.m. and then six grains every two hours. Normal rhythm returned after 33 grains of quinidine. The improvement was immediate and remarkable. Within a week the edema and orthopnea were gone. The vital capacity on August 31, 1944 was 2.4 liters or 56 per cent of normal, and the venous pressure was 10 centimeters of water. On September 5, 1944 the vital capacity was 3.8 liters or 88 per cent of normal. From that time until this report (17 months) there was no return of congestive failure. There was no edema nor enlargement of the liver, but his activities were necessarily restricted.

## REVIEW

In these 15 desperately sick patients (table 1) repeated embolism, long standing auricular fibrillation, marked congestive failure, and conduction defects were not considered contraindications because the danger of death from the condition in each patient was considered greater than the danger of death from the drug. The decision as to whether or not to use quinidine was based upon individual considerations, not upon general contraindications.

## ANALYSIS OF CASES OF SUDDEN DEATH

Sudden death was found as the cause of death in 16 patients with congestive failure, and in 13 patients without congestive failure described in the literature. These were studied as far as data permitted with respect to the etiology of the heart disease, the duration of the auricular fibrillation, the return, or failure to return, to normal rhythm, and the coincident use of digitalis (tables 3 and 4). There was no definite correlation of sudden death with the etiologic type of heart disease. There were as many cases of non-rheumatic as of rheumatic etiology. Death occurred both with and

TABLE III  
Sudden Deaths Following Quinidine in Auricular Fibrillation without Congestive Failure

	Age	Sex	Etiology	Duration	Normal Rhythm	Use of Digitalis	Comments
Kohn and Levine	44	F	Rheumatic mitral stenosis	10 months	Yes—but reverted	Yes	Reverted to auricular fibrillation and given quinidine again.
Kohn and Levine	20	M	Rheumatic mitral stenosis	14 years	Yes—but reverted twice	Yes	Died day after second return to normal rhythm.
Wolff and White	46	F	Hypertension—heart disease	Paroxysmal 4 years—constant 2 months	Yes—but reverted	Yes	"Unlikely her death due to quinidine."
Stroud (2 cases) <sup>18</sup>	—	—	—	—	—	—	No details, but does not believe quinidine responsible.
Newman and Spiro <sup>19</sup>	40	—	Rheumatic mitral disease	Not stated	Yes—died day after	Not stated	
Clark-Kennedy <sup>20</sup>	—	F	Rheumatic mitral stenosis—hypertension	Not stated	No	Yes	Given 1 course of quinidine (180 gr.) without normal rhythm; then digitalis until coupled beats, then immediately quinidine.
Smith and Boland	57	M	Toxic nodular goiter, hypertension	6 months	Yes—died day after	No	Quinidine given post-operatively.
Hewlett <sup>21</sup>	—	—	—	—	—	—	No details (mentioned in footnote).
Berman and Blumenthal	80	M	Coronary artery disease—hypertension	Not stated	No—died first day	Yes—with moderate improvement	
Berman and Blumenthal	60	F	Hypertension	2 weeks	No	Yes	No necropsy.
Berman and Blumenthal	67	M	Coronary artery disease	6 months	No	Yes	No necropsy.
Smith and Clark <sup>22</sup>	22	F	Rheumatic mitral disease	1 month	No	Yes	No necropsy. Died 29 hours after last dose.

TABLE IV  
Sudden Deaths Following Quinidine in Auricular Fibrillation with Congestive Failure

	Age	Sex	Etiology	Duration of Arrhythmia	Normal Rhythm	Use of Digitalis	Comments
Viko, Marvin, and White	—	—	Not stated	Not stated	Yes—died a few hours after normal rhythm	Probable	No details—died suddenly a few hours after normal rhythm appeared—no necropsy.
Viko, Marvin, and White	—	—	Not stated	Not stated	Yes—but relapsed to auricular fibrillation and died	Yes	No details—no necropsy—died three days after relapse while receiving digitalis.
Burwell and Dieuaide <sup>23</sup>	22	F	Rheumatic mitral stenosis	11 years	Yes—died 12 hours after normal rhythm	Constantly	Slight edema—large heart.
Parkinson and Campbell	53	F	Not stated	7 years	Yes—died day after normal rhythm	Not stated	Slight failure.
Parkinson and Campbell	43	M	Syphilitic aortitis	Not stated	No—died while fibrillating	Not stated	Necropsy—no embolism—"increase in ventricular rate to 180 which might have led us to stop quinidine."
Smith and Boland	45	F	Rheumatic endocarditis	6 weeks	Yes—died day after normal rhythm	Not stated	Myocardial insufficiency.
Smith and Boland	53	M	Coronary sclerosis—hypertension	Several weeks	Yes—died soon after normal rhythm	Yes	Necropsy—no embolism.
Maynard <sup>24</sup>	Middle Age	F	Unknown	Not stated	Yes—died 16 hours after respiratory failure	Yes—had improved	After rest in bed, all signs of failure disappeared.
Sappington <sup>25</sup>	50	M	Not stated	Few days	Yes—died day after	Not stated	Extrasystoles before sudden death.
Jamieson <sup>26</sup>	50	M	Uncertain	1 year	Yes—died 10 hours after	Not stated	Necropsy—negative
Jamieson	29	F	Rheumatic mitral stenosis	Not stated	No—died after 2 doses	Not stated	No necropsy. Had syncopal attacks during observation.
Jamieson	60	M	Syphilitic aortitis	1 year	Yes—died 7 days after	Yes	Gross signs of failure disappeared with rest and digitalis. Occasional ventricular extrasystoles before death.
Jamieson	70	M	Arteriosclerosis—hypertension	Not stated	Yes—with prolonged A-V conduction	Yes	Before quinidine had suggestive right bundle branch block—necropsy—negative.
Berman and Blumenthal	71	M	Coronary artery disease	1 year	Yes—died day after	Yes	Improved with digitalis alone.
Berman and Blumenthal	54	—	Hypertension heart disease	3 years	No	Yes	Improved with digitalis alone.
Levy	49	F	Probably rheumatic	Not certain	Yes—died same day	Yes	Improved with rest and digitalis. Edema disappeared. Necropsy—embolism.

without return of the auricular fibrillation to normal rhythm. The arrhythmia had existed for years in some instances, and only a few days or weeks in others. In the 16 patients with congestive failure, quinidine was given in five instances, although improvement had occurred with rest and digitalis. In another, the drug was continued despite a ventricular rate of 180.

### DISCUSSION

The ultimate value of return to normal rhythm in a patient with severe heart disease and long standing auricular fibrillation ordinarily would not be considered great. The established arrhythmia itself is significant of fundamentally serious heart disease. The natural history of the associated heart disease is discouraging with regard to therapy. Death occurs in patients with auricular fibrillation, on an average, a few years after recognition of the arrhythmia. Occasionally a patient may live 10 to 20 years.<sup>7</sup> If auricular fibrillation develops in rheumatic heart disease, the chances of living five years, statistically, are about one to nine.<sup>12</sup> Death is likely to occur from congestive failure, from embolism, from acute carditis, and very rarely from subacute bacterial endocarditis.<sup>5</sup> In certain instances, however, the results from quinidine administration are gratifying.

The inferences from the data in this paper would agree with other opinions that quinidine is a drug feared much more than it deserves to be, and that probably it is not used in many instances where it should be.<sup>18</sup> Certain objections cited against its use are shortcomings, not contraindications. Toxic effects, such as nausea, tinnitus, and diarrhea, if mild, may be ignored. If toxic effects persist, they will disappear with discontinuance of the drug. Another objection, that normal rhythm may not be produced nor maintained can be determined only by a therapeutic trial. There are no convincing data that embolism is a considerable risk. Quinidine is apparently no more dangerous in patients without congestive failure than the natural dangers of the heart condition itself. There should be no objections, therefore, to a trial of quinidine in patients without congestive failure unless conduction defects are present. In such instances, it should not be given. Conduction defects are a definite contraindication at all times unless, as in the two cases reported, the patient is desperately sick. Apparently the only real danger of quinidine is that of sudden death, which is an important factor only in the presence of congestive failure or of conduction defects. Even in the presence of congestive failure the liability of sudden death after quinidine is statistically little more than the natural risk of sudden death from the heart disease itself. If the cases with congestive failure were carefully selected, the risk of sudden death from the drug probably could be reduced to a negligible factor. Among patients with congestive failure who improve adequately with digitalis, and rest, quinidine would seem unnecessary. Had this criterion been observed, several of the 16 sudden deaths could not have been ascribed

to quinidine. For patients with congestive failure who do not respond to digitalis, rest, and other measures, the risk of quinidine may not be as great as the risk of the condition even if conduction defects be present. If conduction defects are not present, there would seem to be no reason why every patient with uncontrolled congestive failure should not be given a test with quinidine. Even if the ventricular rate is slow, reversion to sinus rhythm may relieve the congestive failure. As a paradox to the ordinary concepts, apparently the more desperately sick the patient, the more justifiable becomes the use of quinidine. Ordinarily it is thought that the more severe the heart damage, the greater the contraindication for quinidine. As the risk of the condition rises, however, the relative risk of quinidine decreases. The use of quinidine adds little to the risk of an apparently hopelessly sick person. A return to sinus rhythm cannot, of course, be expected to change the inevitable downward course of progressive heart disease. It can, in certain instances, however, relieve congestive failure not responding to other measures, and can prolong life. The usually accepted contraindications to the use of quinidine, therefore, congestive failure, repeated embolism, long standing auricular fibrillation, and conduction defects are not absolute contraindications. In certain individual instances the danger of the use of quinidine may be less than the danger of the heart condition itself, and quinidine should be given.

#### CONCLUSIONS

1. An analysis of a large number of patients with auricular fibrillation treated with quinidine indicates that the principal hazard of quinidine is that of sudden death, and that the possibility of embolism should not be cited as a danger from quinidine to contraindicate its therapeutic trial.

2. Sudden death, statistically, is not a hazard in the absence of congestive failure.

3. Sudden death is a hazard in the presence of congestive failure, but the increased risk at times may be justified owing to the risk of the heart disease itself.

4. Quinidine is life saving in certain patients with congestive failure, long standing auricular fibrillation, and conduction defects, and these conditions should not be cited as absolute contraindications to the use of quinidine.

5. Quinidine should be given a trial more often in desperately sick patients.

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# BLASTOMYCOSIS: A BRIEF REVIEW OF THE LITERATURE AND A REPORT OF A CASE INVOLVING THE MENINGES \*

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## INTRODUCTION

It is the purpose of this paper briefly to review the pertinent literature on the subject of blastomycosis and to report another proved case of systemic disease with involvement of the meninges. Although blastomycosis is a rather uncommon disease, it is nevertheless a very important clinical entity when it does occur, since the systemic variety usually terminates fatally. Both the systemic and cutaneous forms of the infection can successfully mimic myriad other diseases frequently encountered in the practice of medicine. Therefore, physicians in general should be familiar with the various clinical manifestations of this disease in order to establish an early diagnosis with the aid of the laboratory so as to facilitate the institution of early and effective therapeutic measures in this otherwise chronic and fatal condition.

*Definition.* Blastomycosis is a specific chronic infectious disease caused by the *Blastomyces dermatitidis*.<sup>23</sup> It is characterized by the appearance upon the skin of single or multiple pyogenic granulomatous verrucoid lesions; and systemically by the presence of single or multiple granulomatous lesions in the internal organs. Clinically, we recognize two types of blastomycosis, the systemic and the cutaneous.

*Historical.* The clinical picture of the disease in man was first described by Gilchrist of this country in 1894, at a meeting of the American Dermatological Association.<sup>23, 36</sup> At this time he also demonstrated the responsible organism in stained tissue sections and four years later gave it the name by which it is presently recognized. Since that time, 19 different names have been suggested for this disease,<sup>31</sup> but of all these only three are acceptable today and can be used interchangeably—blastomycosis, North American blastomycosis and Gilchrist's disease. Some of the confusion regarding the terminology is no doubt the result of an inadequate appreciation of the systemic nature of the disease and its various clinical manifestations. However, the widely varying morphology of the organism<sup>4, 48</sup> is more than likely chiefly responsible for the existing confusion. The morphology varies even in the same strain and occasionally different strains can be isolated

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from the same patient in separated lesions.<sup>48</sup> Martin's work has proved that these are all one and the same organism.<sup>20</sup> The contributions of Benham,<sup>4</sup> Martin and Smith<sup>31</sup> Conant and Martin,<sup>13</sup> and L. M. Smith<sup>40</sup> have clarified the situation sufficiently to make possible intelligent case reporting and proper classification of this disease. The serological, morphological and bacteriological studies of these investigators working with various strains of the *Blastomyces dermatitidis* have resulted in the adoption of the previously mentioned uniform and acceptable nomenclature for this disease.

*Geographical Distribution.* In 1939, Martin and Smith reported on 243 proved and presumptive cases of blastomycosis assembled from the literature.<sup>31</sup> All but two of these cases occurred in the United States. England and Canada were the source of these two proved cases. The largest number of cases has been reported from Illinois and Louisiana, but the disease has been encountered in 28 different and widely separated states. Evaluation of the European and South American case reports is difficult and uncertain because of the unsatisfactory classification and method of reporting.<sup>31, 50</sup> Beregoff-Gillow claims that the disease is not at all uncommon in Canada,<sup>5</sup> and the literature contains several case reports originating in that country.<sup>22, 47</sup> The recent literature contains an additional case report from England<sup>1</sup> and one from Australia.<sup>39</sup> These latter claims and reports are in sharp disagreement with the findings of Martin and Smith which indicate that the disease is peculiar to this country.<sup>31</sup>

*Incidence.* The incidence of the disease is greatest in agricultural workers, common laborers, and people who work or live in damp, unhygienic and wooded places.<sup>9, 48</sup> Perhaps this accounts for the fact that males are affected about eight times as often as females.<sup>3, 16, 24, 48</sup> To believe that the negro is exempt from this disease<sup>34</sup> is erroneous because the statistics in any large series of case reports demonstrate that the negro is at least as susceptible as the white to this infection.<sup>8, 9, 16, 50</sup> Any difference that does exist in racial incidence is probably related to the population ratio in the community concerned. It is a disease of the working class and poor people.<sup>27, 48, 50</sup> Although the disease occurs most frequently in the third, fourth and fifth decades of life, no age group is immune.<sup>31</sup> There is a case on record involving a six month old infant and in a case observed by Ormsby the patient was 76 years old.<sup>40, 43</sup>

*Method of Infection.* Although the exact method of infection is not yet clearly understood, it is more or less generally agreed that the organism enters the body either by way of the respiratory tract or through an abraded skin area.<sup>3, 11, 31, 48, 50</sup> On occasion the organism has been found as a secondary invader complicating preëxisting lesions of other disorders, and in other instances the infection had a definite preceding history of trauma.<sup>3, 5, 38, 40</sup> Cases have been reported in which the onset of the illness followed injuries to the skin with such agents as clams, thorns, nails and splinters of wood.<sup>17, 44, 48, 49</sup> Crich reported a case in which the disease occurred after a history of grass-chewing; Robinson observed that the onset of the infection

in his patient followed a slight injury sustained while walking barefoot in a field.<sup>31</sup> Stober reported a large number of cases which occurred in the foreign population in and around Chicago. He was able to recover the organism from a mold which was growing in the damp and dark living quarters of one patient.<sup>48</sup> The large number of cases occurring in the Chicago area suggested the name "Chicago disease,"<sup>50</sup> but reliable investigation proved that the etiologic agent in these cases and Gilchrist's organism were identical.<sup>31</sup> Stober was unable to find any evidence in his series to indicate the direct transmission of the disease from man to man, but subsequent reports confirm this possibility.<sup>48</sup> Evans reported a case of direct transmission as occurring in a physician who injured his finger while performing an autopsy on a case of systemic blastomycosis and subsequently developed a cutaneous lesion at the site of injury.<sup>18</sup> Harding reported another case of possible contagion.<sup>24</sup> His patient was living with a known case of blastomycosis and later developed cutaneous lesions at the sites of skin cuts sustained while shaving.

**Bacteriology.** *Blastomyces dermatitidis* is a fungus which grows as a mold on artificial culture media and in so doing produces budding organisms and mycelia with or without lateral conidia. It is a non-fermenter. When the fresh purulent exudate of the lesion which it produces is mixed with 20 per cent sodium or potassium hydroxide, the organism can be identified easily by microscopic examination as a doubly refractile ovoid or round body with granular cytoplasm. In the same field budding and non-budding organisms are frequently detected and may vary in size from 7  $\mu$ . to 20  $\mu$ . or more.<sup>4, 10, 23, 31, 40, 48</sup> The organism is very widespread in nature and can grow in almost any environment. In systemic cases it can be isolated from the blood, stool, sputum and urine.<sup>48</sup>

**Clinical and Pathological Features.** The cutaneous lesion occurs most frequently on the face and other exposed areas of the body. It may be localized in one area or have a multiple distribution. On the face it commonly attacks the nose, lips, cheeks, forehead and eyelids, but spares the conjunctiva. The lesion first appears as a papular pustule which soon ruptures to develop a friable necrotic crust and slowly increases in size centrifugally. The active margin of the lesion is typically violaceous and elevated one-eighth to three-eighths of an inch over the surrounding skin. As the lesion grows larger the central area has a tendency to heal with fine soft scar formation whereas the margin remains elevated and sharply demarcated from the surrounding normal skin. The crust is easily removed piecemeal with little or no pain and uncovers an almost flat bleeding base with papillary projections which are bathed in serosanguineous exudate and pus. The peripheral area, characteristically, has numerous miliary abscesses which can be seen on careful examination, and exude a thin purulent exudate on slight pressure. Material for smear, culture and biopsy should be obtained from this part of the lesion. The cutaneous lesions are either single or multiple and are usually first seen by the physician when they are several months old

or about one inch in diameter. Single lesions may reach a diameter of eight to 10 inches. The shape of the lesions varies greatly but they are usually rounded, arciform or serpiginous in contour and may be confluent. When the skin is secondarily involved in the systemic variety of the disease, the distribution of the lesions has no special pattern and usually start as deep subcutaneous nodules which soon break down, ulcerate and display the typical elevated violaceous margins. Occasionally, miliary abscesses of the skin and subcutaneous tissue may result in the formation of larger localized abscesses which may contain a quart or more of pus.<sup>8, 38, 40, 41, 48</sup> Although it is still a matter of conjecture, it is generally believed that in the cutaneous form of the disease multiple skin lesions are usually the result of auto-inoculation, and less frequently the result of lymphatic spread.<sup>3, 40, 42</sup>

Forty to 50 per cent of all cases of blastomycosis are probably systemic.<sup>10, 31</sup> In the systemic variety of the disease a pulmonary focus is usually responsible for dissemination of the infectious agent, but it may be the result of improperly treated or neglected cutaneous involvement of long standing. However, it is more common for the systemic type of the disease to have cutaneous manifestations than it is for the cutaneous variety to result in systemic disease.<sup>3, 4, 27, 48, 50</sup> The organism is disseminated by way of the blood stream and lymphatics or else the disease involves adjacent tissues and organs by direct extension.<sup>3, 8, 42, 48, 50</sup> Although the organism has a predilection for the skin, subcutaneous tissue, lungs, bones and joints, no tissue or organ in the body is immune to attack.<sup>5, 31</sup> Blastomycosis of the central nervous system is rather uncommon, and only 16 acceptable cases were found in a comprehensive review of the literature up till 1939, conducted by Martin and Smith of Duke Medical School. The cerebellum, cerebrum or brain stem is usually involved, but occasionally the spinal cord is also attacked.<sup>31, 48, 50</sup> Although single or multiple abscesses in these areas are the general rule, Craig and Carmichael have reported a case of blastomycoma of the cerebellum, and more recently Craig and Dockerty have reported an intravertebral and intrathoracic blastomycoma simulating a dumb-bell shaped tumor.<sup>14, 15</sup> Meningeal involvement is especially uncommon and fewer than 10 possibly acceptable cases are recorded in the literature.<sup>3, 7, 20, 28, 32, 37, 48, 50</sup>

In the systemic disease the lungs are more frequently involved than any other internal organ. Wade and Bel compiled 27 cases from the literature including their own and found that pulmonary lesions existed in 26 instances or 96 per cent of the total.<sup>50</sup> The pathologic lesion in the lungs is very similar to tuberculosis and to make matters even more confusing the two diseases have been known to coexist in the same patient.<sup>24, 50</sup> Medlar<sup>35</sup> and D'Aunoy and Beven<sup>16</sup> do not believe that even the most capable pathologist is able to make the differentiation from a histopathologic section unless the organism can be identified. Baker believes that the pathology of the two conditions is very similar but insists that the differentiation can be made on a histopathologic basis.<sup>3</sup> On gross examination of the lungs at autopsy,

the process appears to be bronchopneumonic in nature with small and large abscesses scattered throughout the pulmonary tissue. Localized areas of consolidation, caseation and nodule formation are frequent. The pleura is often thickened and adhesions occur between the parietal and visceral surfaces. Histologically, the lesion contains miliary abscesses composed of blastomycetes, many polymorphonuclear elements, multinucleated giant-cells, round cells, epithelioid cells, plasma cells, occasional eosinophiles and much necrotic material.<sup>3, 16, 35, 40, 48, 50</sup> The predominance of polymorphonuclear cells and the occurrence of microscopic abscesses should suggest the diagnosis of blastomycosis rather than tuberculosis even in the absence of demonstrable organisms. The pathology is essentially the same in all involved organs and tissues. Bones and joints are affected in 50 to 60 per cent of the studied cases with most frequent involvement of the vertebrae, skull and ribs.<sup>27, 31, 50</sup> The process usually starts in the epiphyseal portion of the bone and is overwhelmingly destructive in nature. It commonly ruptures into the neighboring joint. There is usually an accompanying periostitis.<sup>27, 48</sup>

*Signs and Symptoms.* There are no characteristic signs and symptoms of the systemic form of the disease since they depend on the special organ or organs involved and the degree of involvement of each. However, it may be well to note that in general the signs and symptoms will be the same as those found in any other generalized, chronic infectious and debilitating illness. The onset of systemic blastomycosis is associated with signs and symptoms referable to the respiratory tract in more than 50 per cent of the cases and it usually follows a steady downward course with chills, fever, leukocytosis and anemia.<sup>31, 48, 50</sup> Skin lesions are usually painless unless they invade deeper tissues.

*Diagnosis.* Although a presumptive diagnosis of the disease can be made on the basis of the overall clinical picture and by inspection and examination of typical skin lesions when they exist, it is necessary to resort to laboratory aids in order to establish the diagnosis beyond question. To make an unequivocal diagnosis the organism must be identified in a direct smear from the available lesion, grown on suitable culture media and a tissue biopsy must reveal the typical histopathology including the etiologic agent. Baker believes that a tissue biopsy which meets these requirements is sufficient for absolute diagnosis.<sup>3</sup> The complement fixation test described by Martin<sup>20</sup> and the skin test with autogenous or stock vaccine can be resorted to in obscure lesions of internal organs when suitable material for direct examination can not be obtained.<sup>31</sup> Dulaney suggests that the complement fixation test must be done with titrated serum to be specific or else closely related organisms may give falsely positive results.<sup>17</sup> Despite all these valuable aids, in many cases the final diagnosis is made only after examination of the autopsy material by the histopathologist.

*Differential Diagnosis.* The clinical picture of cutaneous and systemic blastomycosis is never so clear that it can not be confused with many other similar diseases. In making the diagnosis of blastomycosis it is necessary

to consider all the other diseases caused by fungi, especially torula, actinomycosis, South American blastomycosis, chromoblastomycosis, coccidioidomycosis, tinea barbae, and in addition tuberculosis, tularemia, syphilis, osteomyelitis, anthrax, bromoderma, squamous and basal cell carcinoma and lupus vulgaris. In this hospital it has been most often confused with squamous and basal cell carcinomas, tuberculosis, syphilis and lupus vulgaris. When the lesions occur in the genitourinary tract and on the external genitalia, it is necessary to consider all the venereal diseases, especially in the colored race. These are but a few of the conditions which blastomycosis can mimic and in all these cases the correct diagnosis can be established beyond question only through the intelligent utilization of the proper laboratory aids.<sup>33</sup>

*Prognosis.* The prognosis in the cutaneous type of blastomycosis is good as far as life expectancy is concerned, but it is generally very resistant to treatment. Although many cures are reported, remissions after apparent cures are frequent and the disease tends to recur and run a very chronic course.<sup>3, 23, 31, 38, 40, 44, 48, 51</sup> Millard and Goddard followed a lesion on the face for 20 years, and in this hospital a lesion on the face and forehead has been followed for 18 years.<sup>31</sup> The outlook in the systemic variety of the disease is uniformly bad and the mortality rate is accepted as 90 per cent or more within three to five years after onset of the illness.<sup>12, 24, 31, 40, 48, 50</sup> There are several cases on record in which real cures were reported, but the results in the majority of these instances must be accepted with reservation since the details are either inadequate or the period of observation too short to evaluate properly the efficiency of the various therapeutic measures employed. Stober reported two cases and Baker another in which the cure was probably the result of the immunologic response of the host, and it is entirely possible that at least some of the reported cures are the result of this same mechanism rather than the therapy employed.<sup>3, 48</sup> A great deal of evidence has accumulated in the literature which indicates that the course and ultimate outcome of the disease in both forms depends in a large measure, if not entirely, on the allergic or immunologic response of the host to the infection.<sup>11, 17, 31</sup> Martin and Smith have shown that the level of the antibody titer of the complement fixation test can be used to indicate the degree of infection in systemic cases and to prognosticate safely the ultimate outcome.<sup>31</sup> A high antibody titer and a negative skin test indicate a very unfavorable prognosis. A more favorable course can be anticipated when the skin test is positive and the complement fixation test is negative.<sup>13</sup> Although the diagnosis of blastomycosis is beyond doubt frequently overlooked, the immune response of the host to the invading organism is probably more responsible for the comparative paucity of recognized cases.

*Treatment.* In general, the treatment of cutaneous and systemic blastomycosis is very unsatisfactory and leaves much to be desired. The possibility of successful prophylaxis is discouraging because of the widespread distribution of the organism in nature, but the maintenance of hygienic conditions and good general health should contribute to a decreased in-

cidence of the disease. Although the cutaneous lesions will temporarily respond to a multitude of therapeutic agents, recurrences are frequent after cessation of active therapy. Gilchrist used potassium iodide empirically with some success and since that time the iodides have been used in massive doses orally and intravenously with variable results.<sup>12, 22, 24, 27, 31, 40, 48, 51</sup> When the lesions do not respond to this form of therapy, Ormsby suggests the intravenous use of arsphenamine to render the organism more susceptible to the action of the iodides.<sup>40</sup> Several of his cases were benefited with this form of therapy, but Clarkson and Barker report a therapeutic failure.<sup>12</sup> In an apparently futile effort to discover a consistently effective and dependable therapeutic measure for the cutaneous type of the disease, a multitude of remedies for local and systemic administration have been recommended by various individuals. Among these suggested remedies are copper sulfate, silver nitrate, carbon dioxide snow, gentian violet, various sulfa drug preparations, cauterization, curettement or local surgical excision of the lesions, radium implantation and roentgen-ray therapy.<sup>1, 12, 23, 25, 27, 31, 40, 48, 50, 51</sup> With all of these measures recurrences are frequent and the results are generally inconstant. Garcia believes that roentgen-ray therapy is the most effective and promising therapeutic procedure currently available.<sup>21</sup> He has obtained good results in early lesions, but the results in larger and older lesions are uniformly poor.

The treatment of the systemic disease is even more unsatisfactory. Iodides in large doses orally and intravenously have proved of very questionable value in most cases and in some there is incontrovertible evidence that actual harm accrued from the use of the drug. If the patient's allergic response outweighs the immune response to the infection, then iodides are contraindicated.<sup>31</sup> If the patient is skin-tested and found to be hypersensitive, then a gradual course of desensitization should be undertaken and only after that may small amounts of iodides be given with safety. Christensen and Hektoen<sup>11</sup> recommended vaccine therapy for the disease in 1906, and Stober<sup>48</sup> later used it successfully in two cases. From all present indications a combination of iodides and vaccine therapy seems to be the best available treatment.<sup>17, 31</sup> Immune serum, tincture of iodine intravenously and recently rectal instillations of ether have been credited with cures.<sup>6, 19, 30, 45</sup> In our case ether was of no value. Herrell and his coworkers<sup>20</sup> discourage the use of penicillin in this disease, and Alvarado<sup>2</sup> found that in one of his cases the use of massive doses of penicillin completely failed to alter the course of the disease.

#### CASE REPORT

A 42 year old colored male laborer was admitted to Charity Hospital in a comatose condition. The admission diagnosis was "rupial syphilis."

Present Illness: The present illness began two and one-half months prior to admission, when the patient began complaining of fever associated with malaise and progressive weakness. About one week after the onset of these symptoms a small

red papule appeared on the ala nasi of the left side. This was followed in a few days by the appearance of similar lesions elsewhere on his face and forehead. During the next two to three weeks the lesions enlarged and suppurated, discharging thick yellow pus. Throughout this period he was confined to bed because of extreme weakness and gradually lapsed into coma about one and one-half months after the onset of his illness. He remained in this condition for 17 days, during which time lesions similar to the ones described on the face appeared on the upper and lower extremities. These latter lesions began as hard subcutaneous nodules. During this episode a physician was called to see the patient and a spinal tap was performed. Following examination of the spinal fluid, the patient was treated with tryparsamide intravenously. An explanatory note sent by the local physician with the patient



FIG. 1. Photograph of patient's face on admission.

indicated that he was treating the patient for syphilis of the central nervous system. He seemingly improved on this therapy and regained consciousness for about seven days. However, he again lapsed into coma and was admitted to the hospital 12 days later.

Past History: non-contributory.

Family History: non-contributory.

Social History: For two weeks prior to the onset of his present illness he worked in a plant which processed bagasse for building material.

Physical Examination: The temperature was 99° F., the pulse 90, and respirations were 24. The blood pressure was 130 mm. Hg systolic and 90 mm. diastolic.

The patient was a fairly well-developed colored male of stated age, poorly nourished and comatose. There were numerous rounded ulcerating lesions present on the nose, cheeks, forehead, chin and eyelids (figure 1). They were about two centimeters in diameter and some lesions were confluent. The conjunctiva of the eye was not involved. The lesions were most numerous about the nose, and the left ala nasi was partially destroyed. A thick brown necrotic crust covered each lesion

and the sloping edges were raised and sharply demarcated from the surrounding skin. Beneath the crust numerous papillary projections were seen. These were covered with serosanguinous exudate and frank pus. Pressure on the peripheral part of the lesion caused thick pus to exude from numerous pin-point foci. The dorsum of the hands, the fingers and the upper and lower extremities were involved to a lesser degree. In these locations the lesions were deeper seated.

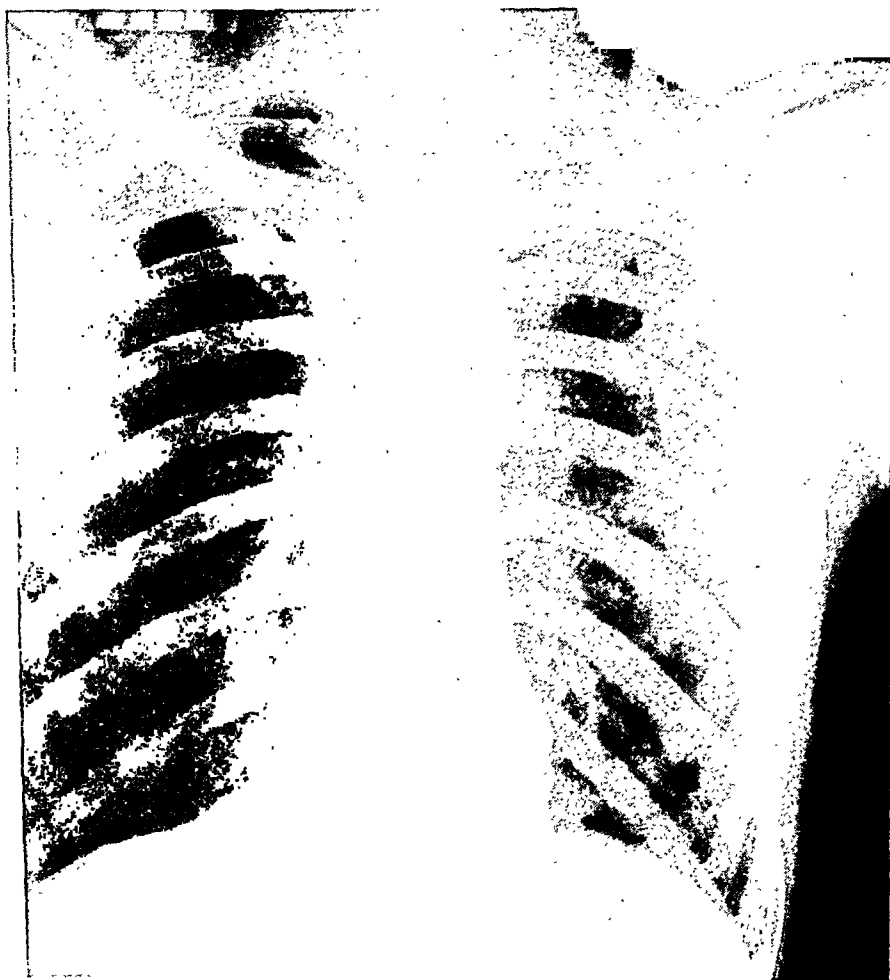


FIG. 2. Admission roentgenogram of chest. Note area of irregular homogeneous infiltration in peripheral area of second anterior interspace on the left.

The heart, lungs and abdomen were clinically negative. The right testicle was enlarged (4 by 6 cm.) and firm. The epididymis was indurated. The extremities were spastic and bilateral pes cavus was present. Both pupils were round and equal in size and reacted sluggishly to light. Marked nuchal rigidity was present, as well as positive Kernig and Brudzinski signs. All other reflexes were absent and the Babinski reaction was negative.

Laboratory Data: Hemoglobin 13.5 gm.; red blood count 4,300,000; white blood count 14,500; differential count: polymorphonuclear cells 82 per cent, lymphocytes 14 per cent, monocytes 3 per cent, basophiles 1 per cent. Urine was negative. Serology: Kline reaction was negative on two occasions. Blood cultures were negative for all organisms including fungi on two occasions.



Spinal fluid: pressure 230 mm. Queckenstedt negative. Fluid was clear and colorless. Cell count: 40 lymphocytes. Chemical determinations: protein level 116 mg.; sugar level 32 mg.; chloride level 583 mg. Kline test was positive on three occasions. Kolmer test was negative on three occasions. Colloidal gold curve: first zone on three occasions. Bacteriology: negative gram stain, methylene blue and sodium hydroxide preparations on numerous examinations. Cultures: negative for all organisms including fungi on four occasions.

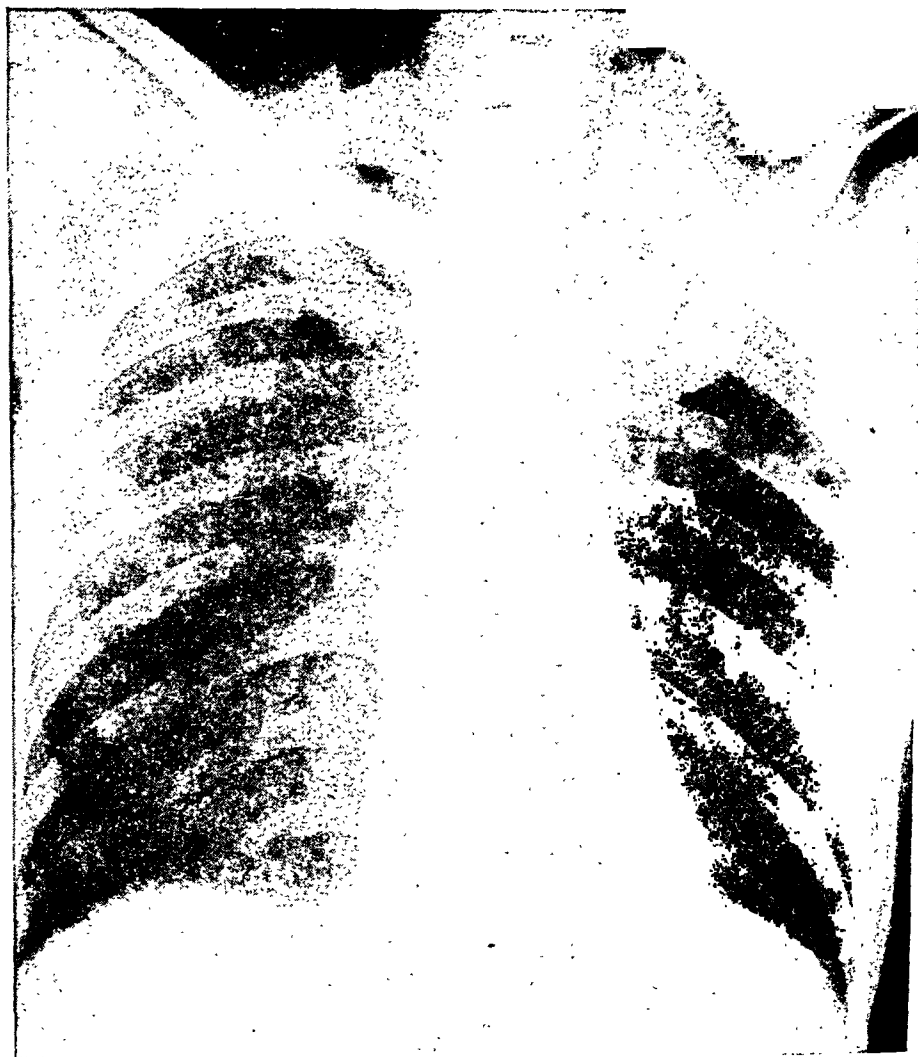


FIG. 3. Roentgenogram of chest six days before death. Scattered infiltration throughout both lung fields with evidence of thickened pleura on the left.

Smear of lesion: Direct microscopic examination of the material obtained from the lesion and mixed with 10 per cent sodium hydroxide revealed numerous budding and non-budding doubly refractile rounded and ovoid bodies. These varied from the size of a red blood cell to  $20\mu$  in diameter.

Culture of exudate: On Sabouraud's glucose agar the material obtained from the lesion had the cultural characteristics of *Blastomyces dermatitidis*.

Biopsy examination: Histopathologic examination of a piece of tissue obtained from a lesion on the nose showed the typical microscopic picture and numerous organisms were identified. The *Blastomyces dermatitidis* was present in the necrotic material and also in giant cells.

Complement fixation test: Dr. Donald S. Martin of Duke Medical School reported that the test was positive. It was 4 plus in a 1:8 dilution of the serum and 2 plus in a 1:16 dilution.

Roentgenological examinations: Roentgenograms of the thoracic and lumbar vertebrae, hands and skull were negative. Three days after admission a roentgenogram of the chest (figure 2) revealed a possible irregular homogeneous infiltration

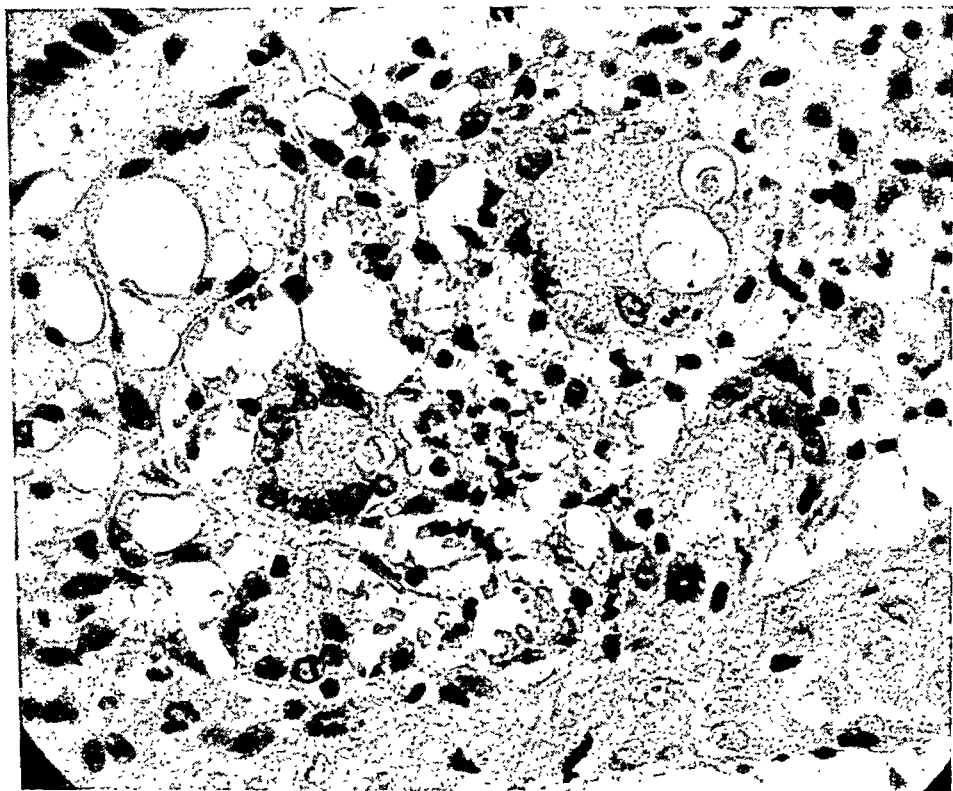


FIG. 4. Photomicrograph of typical skin lesion with blastomycetes in multinucleated giant cells. ( $\times 378$ .)

in the second anterior interspace on the left. Six days before the patient died a roentgenogram of the chest revealed scattered infiltrations throughout both lung fields, but most marked on the left where there was also evidence of pleural thickening (figure 3).

Course in the Hospital: The patient had a low grade fever while in the hospital which was more elevated for the two days preceding death. He remained comatose or semiconscious during his entire hospital stay. Ether in oil was administered per rectum daily and the cutaneous lesions were likewise cleansed with ether and a 1 per cent solution of copper sulfate. This therapy plus the usual supportive measures had no appreciable effect on the course of his illness which was progressively downward and the patient died on the twenty-eighth hospital day. Oral and intravenous iodide therapy was instituted two days before death occurred.

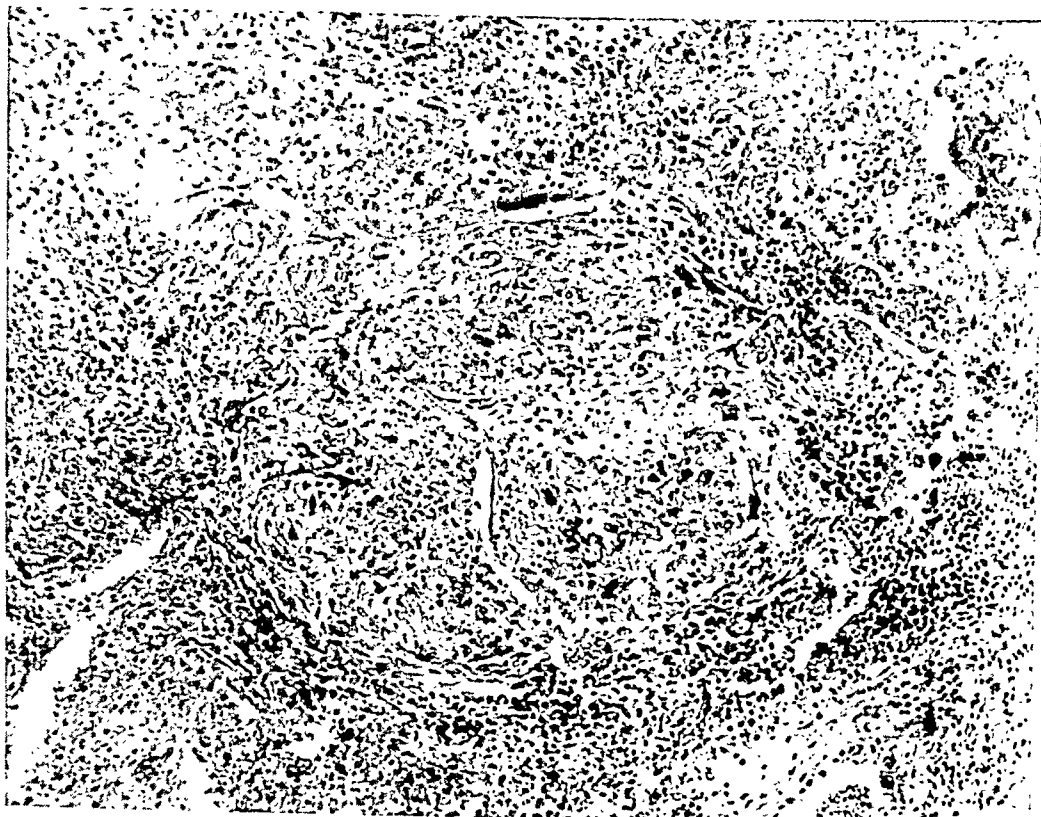


FIG. 5. Photomicrograph of lesion in lung showing "tubercle" formation. Note the prominent epithelioid reaction. Organisms were present in this lesion. ( $\times 110$ .)

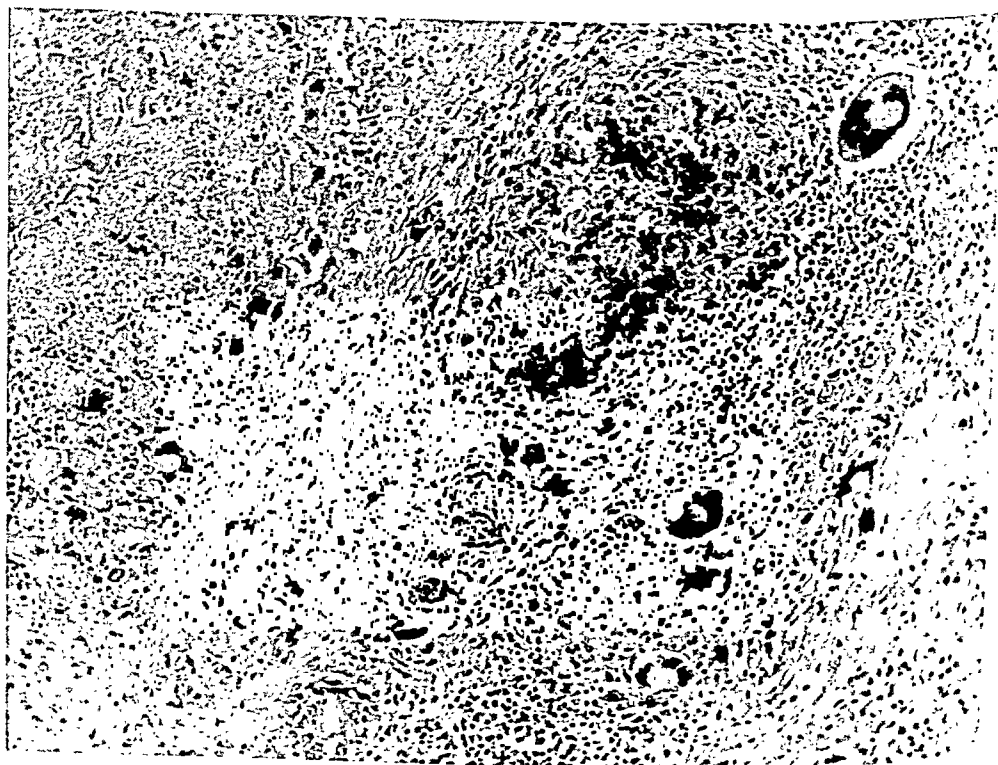


FIG. 6. Photomicrograph of lesion in leptomeninges. Note caseous-like necrosis to the left and liquefaction necrosis in center of epithelioid cells in upper right. Multinucleated giant cells were numerous in some areas. ( $\times 110$ .)

Autopsy findings: Only the skin, lungs and meninges were involved at postmortem examination. The appearance of the skin lesions was essentially the same as the admission note described them. Microscopic examination of a section obtained from a typical lesion revealed numerous miliary abscesses composed of polymorphonuclear cells, round cells, much necrotic material and a generous sprinkling of budding and non-budding blastomycetes. Some of the organisms were included in giant cells (figure 4). Scattered throughout the upper lobes of both lung fields were innumerable sharply defined firm gray nodules about 2 to 3 mm. in diameter. The cut surface of the middle and lower lobes revealed numerous elevated gray granular areas with irregular outlines. Some measured as much as 1.5 cm. in size and others tended to become confluent. There were multiple thick adhesions extending over an area of 4 by 6 cm. on the superior and lateral surface of the apex of the left upper lobe. Microscopic examination of pulmonary sections revealed the typical histopathology (figure 5). *Blastomyces dermatitidis* and a hemolytic streptococcus were cultured from the pulmonary exudate. The meninges of the brain and spinal cord were also involved. There was an extensive basilar exudate of yellow firmly attached material and marked thickening and proliferation of tissue in the region of the foramen of Magendie and the two of Luschka. All of these apertures were completely occluded. The leptomeninges and the dura in the region of the foramen of Magendie were so firmly attached that removal of the brain was accomplished only after the adherent area was excised with a knife. Microscopic examination of sections of the meninges revealed the typical histopathology (figure 6), and a pure culture of *Blastomyces dermatitidis* was grown from the basilar exudate.

No other organs and tissues were involved.

#### DISCUSSION

Even without the benefit of laboratory aids, the rather typical clinical picture in this case strongly suggested the diagnosis of systemic blastomycosis with meningeal involvement. The positive spinal fluid Kline reaction and lack of knowledge of this disease entity were in all likelihood responsible for the initial erroneous diagnosis of syphilis. In view of the negative blood Kline reaction and the high spinal fluid protein level, acceptance of the more specific and repeatedly negative Kolmer test, and rejection of the more sensitive Kline test on the spinal fluid as falsely positive is justifiable. Awareness of the possibility of the disease entity and utilization of proper laboratory aids established the diagnosis beyond doubt before postmortem examination. Whether the meninges were involved by hematogenous spread from a pulmonary focus or by lymphatic and venous return from the lesions on the nose and eyelids is a debatable matter. However, it does seem rather unusual that the meninges which are involved only infrequently should be attacked and other organs and tissues which are more common sites of the infection should be spared. Clarification of this point must await further investigation. Although it is difficult to draw any worthwhile conclusion from the experience with one case, especially one with such a poor prognosis from the start, the value of ether therapy in this disease appears to be quite doubtful. The death of the patient following so soon after the institution of iodide therapy may be a coincidence, but certainly leaves room for speculation. This may well have been another case in which iodide therapy was

not only valueless, but probably contraindicated and caused an acute exacerbation of the disease process with rapid death of the patient.

### CONCLUSION

For a long time after Gilchrist's original description of the disease, blastomycosis was considered a dermatological curiosity and as a result most of the advances in the field were more or less limited to the contributions of dermatologists, bacteriologists and pathologists. Subsequently, the investigations of Stober, Wade and Bel, D'Aunoy and Beven and many others revealed the systemic nature of the disease and stressed its frequency. The most outstanding contributions to the subject in recent years have been the result of the comprehensive investigations of the group at Duke Medical School. It was largely through their efforts and Benham's, as previously indicated, that the confusion concerning the nomenclature of the disease and the identity of the organism was overcome. Earlier investigators suspected the importance of the immunologic response of the host and its pathologic and therapeutic implications, but it remained for them and Dulaney to offer an acceptable explanation regarding this aspect of the disease. Although our failure to appreciate the systemic nature of the disease has now been largely overcome, our knowledge and real understanding of this important clinical entity are still very meager and await further clinical and laboratory research. When the pathology, pathogenesis and immunologic features of the disease are more clearly understood, then we may hope to find an effective therapeutic agent. In addition it is necessary to define accurately what is meant by a cure in order to evaluate intelligently claims concerning new therapeutic agents. Many drugs have erroneously been credited with therapeutic value because the period of observation has been too brief or the natural course of the disease and the immune response of the host have not been considered. In the meantime, physicians should be sufficiently aware of this clinical entity to attempt an early diagnosis so that otherwise ineffective therapeutic measures may prove of some value in curing the cutaneous form of the disease and possibly reducing the mortality rate in the systemic variety. As physicians become more familiar with the clinical picture of this disease, many cases of blastomycosis will no doubt be recognized and correctly diagnosed in heretofore supposedly immune sections of the country.

### SUMMARY

1. A review of the literature on the subject of blastomycosis has been presented.
2. Another case of systemic blastomycosis with meningeal involvement has been added to the literature.

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# THE CLINICAL AND ROENTGENOLOGIC DIAGNOSIS OF PERICARDIAL EFFUSION \*

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PERICARDIAL effusion frequently presents a confusing clinical and roentgenological picture. The multiplicity of diagnostic criteria is indicative of the troubled attitude towards this question. Differential diagnosis may be further complicated by pleural effusion or other basilar pulmonary disease.

The principal causes of massive pericardial effusion are rheumatic fever and tuberculosis. Lupus erythematosus disseminata, pyogenic infections, malignant disease, myxedema, and the terminal phase of cardiorenal failure are less frequent etiologic agents.

The symptoms noted with pericardial effusion may vary considerably, and may be absent until the effusion produces a tamponade effect. The most common complaint is precordial discomfort or a sense of weight substernally. Relief is often sought by assuming an upright position inclined forward. Dyspnea may be distressing, and cyanosis of the face and distention of the neck veins are common. There may be some dysphagia, an irritative cough, and a somewhat anxious facies.

The physical signs include a broadened area of absolute cardiac dullness. The shape of the heart as outlined by percussion has been likened to a water bottle. Friction rubs which may diminish or disappear when the visceral and parietal layers of pericardium are separated are considered diagnostic. Conner<sup>1</sup> reports a high incidence of persistent pericardial friction rubs in patients with large pericardial effusions. In the absence of friction rubs the only auscultatory finding is the muffled and distant character of the heart sounds at the apex. As a rule the sounds are louder with the patient in the erect position. The second pulmonic sound may be accentuated. Dullness and bronchial breathing in the left infrascapular area (Ewart's sign) are often noted. The pulse may be paradoxical.

Electrocardiographic examination may reveal changes in the S-T segments and the T-waves. Low voltage may exist in the presence of a large effusion. No definitely characteristic pattern has been described.<sup>2</sup>

The radiologic recognition of hydropericardium is admittedly difficult. Roesler estimates that the smallest quantity of fluid which might be recognized in an adult is 250 c.c. The only change anticipated with so small an effusion is straightening of the left cardiac border, but inasmuch as this may occur in normal individuals, the value of the sign is questionable. A collection of fluid might be suspected if the usually dorsal concave surface of the

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inferior vena cava as seen in the oblique projections is replaced by a convex bulge. This, too, is a difficult sign to evaluate.

Serial studies for rapid changes in the size of the heart prove helpful if there is no other factor to explain the change. Rapid recession likewise might be indicative of a resorbing pericardial effusion. Disproportionate widening of the upper cardiac contour may occur with the patient in the recumbent position because of the displacement of fluid within the pericardial sac. Examinations for this purpose must be conducted with the same physical factors in both the erect and supine positions. Diminution in the amplitude of pulsations over the lower aspect of the heart shadow with normal or overactive basal pulsations is considered suggestive but not conclusive. Palpation of the apex beat under fluoroscopic observation to determine if an apical impulse can be located well within the left border of the heart shadow has been recommended.

None of the clinical nor roentgenologic criteria is considered absolutely diagnostic. It is most difficult to make a clear differential diagnosis between cardiac dilatation and pericardial effusion, and the presence of basilar pulmonary opacities further complicates matters. In many instances the diagnosis is simply overlooked. In view of recent advances in sulfonamide and penicillin therapy in selected cases,<sup>4</sup> as well as the symptomatic relief which might be afforded the patient by aspiration, it is important to establish a diagnosis as quickly as possible.

Recently a patient diagnosed as having a left pleural effusion was referred for roentgenographic examination of the chest immediately after a left thoracentesis. The tap had been performed through the usual approach beneath the angle of the left scapula. A hydropneumopericardium was demonstrated roentgenologically, thereby establishing the diagnosis of pericardial effusion beyond doubt.

The induction of hydropneumopericardium is a well established therapeutic procedure in the treatment of tuberculous pericarditis. The studies of Adcock, Lyons and Barnwell on the circulatory effects produced in a patient with pneumopericardium are likewise indicative of the safety with which the procedure may be instituted and point out the limits of tolerance.<sup>5</sup> However, no recommendation of the use of artificially induced hydropneumopericardium as a diagnostic procedure was found in our review of the literature. Encouraged by our accidental finding, we proceeded with the method in the next four patients diagnosed as having pericardial effusions and are satisfied that it is a reliable diagnostic aid.

Hydropneumopericardium presents a roentgenologic appearance which cannot be mistaken, and has the advantage of being equally positive in the presence of concomitant pleural effusions or other basal pulmonary disease. The fluid level is confined within the pericardial sac, and may be demonstrated in the frontal and lateral projections. Fluoroscopic examination reveals the waves produced by the heart action, a conclusive proof of hydropneumopericardium.

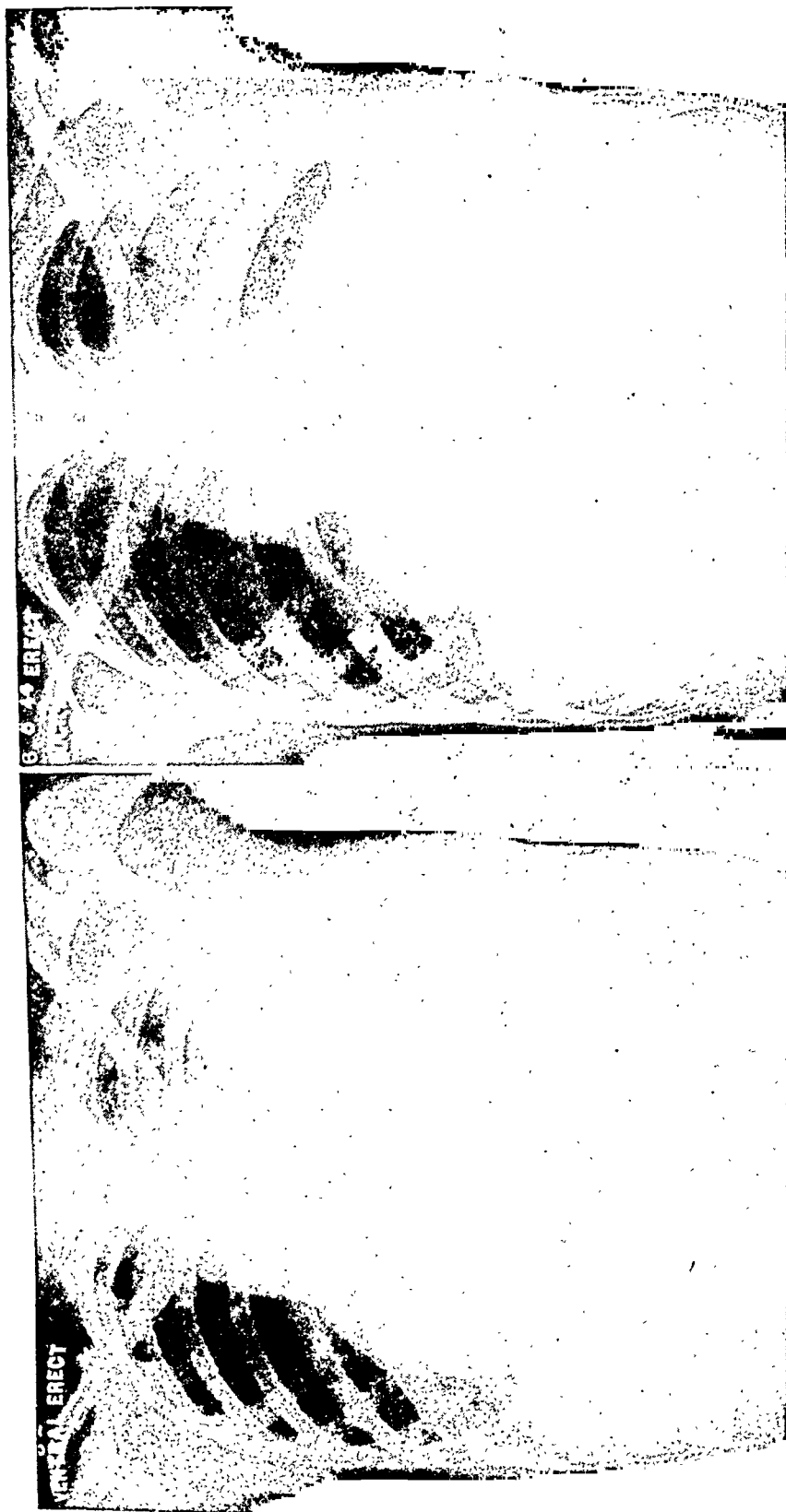


Fig. 1 A. Case 1. Teleroentgenogram revealing a left pleural effusion completely obscuring the left border of the heart. The right cardiophrenic angle is rather acute.

Fig. 1 B. Hydropneumopericardium induced by the removal of 700 c.c. of serosanguinous fluid and the instillation of 100 c.c. of air. Fluid levels are present to the right and left of the midline within the pericardial sac.

There were 13 patients with massive pericardial effusion in the present series. Hydropneumopericardium was induced as a diagnostic procedure in the last five patients. Six had rheumatic pericarditis, two had lupus erythematosus disseminata, two had carcinomatous metastases, two had bacterial pericarditis, and one had cardiorenal failure. Of the five patients who were subjected to hydropneumopericardium, two had rheumatic pericarditis, two had lupus erythematosus disseminata and one had carcinomatous metastases. The relief afforded these people by the aspiration of pericardial fluid was noteworthy.

We prefer to aspirate the pericardial sac through the xiphoid area. The procedure is simple and well tolerated. Should the epicardium be pierced by the advancing needle point, the patient complains of a sharp pain which is a warning to withdraw the needle slightly. The needle is inserted in the space between the ensiform cartilage and the left costal margin, and is directed backward, upward and toward the left, traversing considerable ligamentous tissue before entering the sagging pericardial sac. This long tract serves to hold the needle firmly in place during the withdrawal of fluid. We have obtained over 1000 c.c. of fluid with this method. Our usual practice is to aspirate as much fluid as is indicated by conditions present at the time, then to instill about 100 c.c. of filtered air, and to follow this by roentgenologic examination.

Pericardial fluid may be aspirated from the apical region. When the needle is introduced into this area, fluid is obtained as soon as the needle traverses the anterior thoracic wall. The needle lies but a short distance in the chest wall, and is held steady with difficulty. Moreover, with further insertion the contracting surface of the heart is reached. Conner<sup>1</sup> has shown that even in the presence of extensive pericardial effusion the heart floats in the sac so that it remains in close apposition to the chest wall while the fluid gathers posteriorly, inferiorly and laterally to the heart. It is usually possible to obtain only a small amount of fluid through this approach.

The posterior or lateral thoracic approach recommended by Conner has the disadvantages that lung may be penetrated and that pleural fluid might be aspirated if a pleural effusion is present.

Three illustrative cases are reported.

#### CASE REPORTS

*Case 1.* E. W., female, aged 16 years, had rheumatic fever as a child. Mitral and aortic stenosis and insufficiency were diagnosed at the age of nine years. She was admitted to the Jewish Hospital on December 27, 1943 with subacute bacterial endocarditis confirmed by several positive blood cultures for *Streptococcus viridans*. She responded to penicillin and heparin therapy and was discharged on April 16, 1944 apparently cured of the bacterial infection.

During June 1944 she complained of lower abdominal pain radiating to the epigastrium, both shoulders and the back. Her temperature rose to 102° F., and she became dyspneic and orthopneic. On readmission her neck veins were distended. The apical impulse was palpable in the sixth interspace in the anterior axillary line.

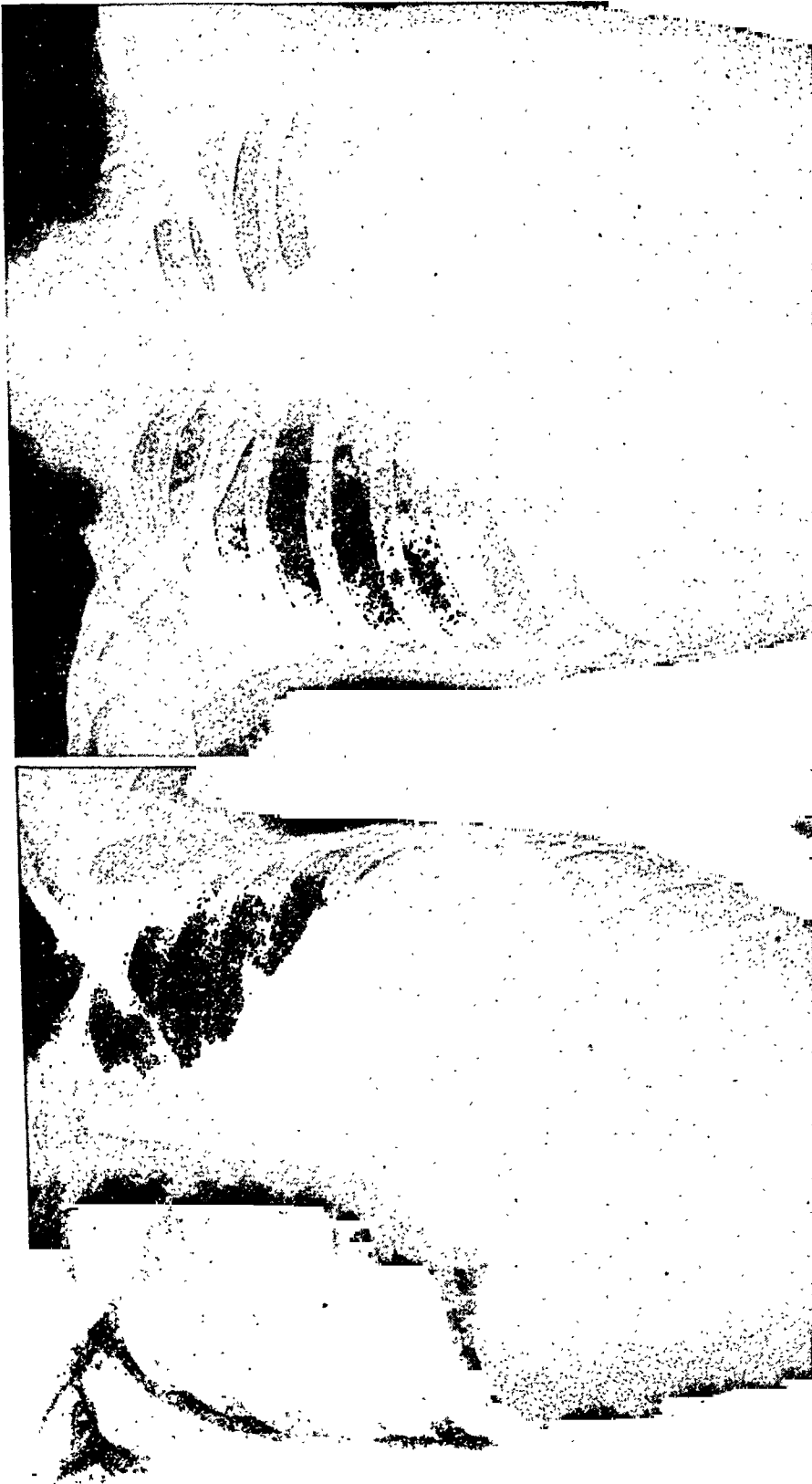


FIG. 2 A. Case 7. Teleroentgenogram revealing diffuse cardiac enlargement. Fluoroscopic inspection revealed diminution of the pulsation of the heart borders. Examination in the right anterior oblique position showed the barium-filled esophagus to assume a smooth, gentle arcuate configuration but no posterior displacement such as might be due to left atrial dilatation.

FIG. 2 B. Teleroentgenogram after the induction of hydropneumopericardium showing fluid levels within the pericardial sac.

There was increased precordial flatness extending from the right midclavicular line to the left anterior axillary line. The heart sounds were distant and the murmurs were only faintly audible. No friction rub was heard. There were dullness, bronchial breathing, and crackling râles over the left lung base posteriorly. Dullness and distant breath sounds were also present over the right base. The liver was palpable three fingers' breadth beneath the costal margin. Her pulse was paradoxical. The clinical diagnosis was active rheumatic carditis with congestive heart failure and bilateral pleural effusion.

Pericardial effusion was not suspected until a thoracic aspiration, in which 600 c.c. of serosanguinous fluid were removed from the left chest, was shown roentgenologically to have produced inadvertently a hydropneumopericardium. A second aspiration was performed the next day again using the posterior thoracic approach and 100 c.c. of filtered air were injected into the pericardial sac.

Roentgenologic examination before the pericardial aspiration showed the heart to be enlarged in all diameters. The lower margins of the heart silhouette were obscured by the bilateral pleural effusions. No undue broadening of the base of the heart was noted. Fluoroscopic inspection before aspiration was not considered indicative of pericardial effusion. The cardiohepatic angle at that time was acute, and after the removal of pericardial fluid it became almost perpendicular. Fluoroscopic examination after the instillation of air into the pericardial sac revealed characteristic waves caused by the heart action. Fluid levels were present both to the right and left of the midline within the pericardial sac, confirming the diagnosis of pericardial effusion.

From June 2 to June 22, 1944, following the pericardial aspirations and salicylate therapy, the heart became smaller and the patient was discharged markedly improved.

*Case 7.* J. M., female, 34 years old, was admitted to the Hospital because of pain in the chest, dyspnea, orthopnea and irregular fever of several weeks' duration.

Five years previously she had had a red scaling rash over her face and both arms which lasted seven months and left the skin somewhat thickened. A diagnosis of lupus erythematosus was made at that time. One year before the present admission she had a siege of high fever lasting five weeks, associated with persistent sore throat and enlargement of the cervical and axillary glands. She never fully recovered and continued to have a low grade fever associated with pain, swelling and stiffness of almost all her joints. Interosseous atrophy of the hands appeared, together with loss of elasticity of the skin of the hands, forearms and face. One month before the present admission a cough developed, her temperature rose to 103° F. daily and she became progressively more dyspneic and orthopneic.

Physical examination revealed an emaciated young woman with thinning of the skin of her face, forearms and hands. The skin had a parchment-like smoothness. The loss of elasticity was so marked that she could not open her mouth more than an inch. There was flatness posteriorly over both lung bases, more marked on the left side. Loud bronchial breathing with fine moist râles was heard over the lower two thirds of the left chest, while at the right base there were distant breath sounds with a few moist râles. The heart rate was rapid. The apical sounds were distant and there was a gallop rhythm. The second pulmonic sound was accentuated. The area of absolute cardiac dullness extended over the entire lower half of the anterior chest. The pulse was paradoxical, disappearing on deep inspiration. The neck veins were distended and the liver was felt two fingers below the costal margin.

A teleroentgenogram made one year previously showed no evidence of cardiac or pulmonary disease. A second examination made during the present admission revealed a definite increase in the size of the heart, with bulging of the left cardiac border. The right side of the heart was not unduly prominent. The cardiohepatic angle was acute. Fluoroscopic observation showed diminution in the amplitude of

Case No. and Etiology	Age and Sex	Dyspnea	Orthopnea	Distended Neck Veins	Enlarged Liver	Apical Impulse	Precordial Absolute Dullness	Diminished Heart Sounds	Friction Rub	Para- doxical Pulse	Ewart's Sign	Pleural Effusion	Hydro- pneumo- peri- cardium Induced
I Rheumatic	F 16	+	+	+	+	+	extensive	+	0	+	+	Left	+
II Rheumatic	M 19	+	+	+	+	+	extensive	0	+	+	+	Right and Left	+
III Rheumatic	M 8	+	0	+	+	0	extensive	+	+	0	+	None	
IV Rheumatic	M 14	+	0	+	+	not recorded	extensive	0	+	not recorded	+	Right	
V Rheumatic	F 8	+	+	+	+	diffuse	extensive	0	+	not recorded	+	None	
VI Rheumatic	M 12	+	0	+	+	diffuse	extensive	+	+	not recorded	+	None	
VII Lupus Ery- thematosus	F 34	+	+	+	+	0	extensive	+	0	+	+	Right and Left	+
VIII Lupus Ery- thematosus	F 18	+	0	+	+	0	extensive	+	0	+	+	Right and Left	+
IX Staphylococcus	F 13	+	0	+	not recorded	not recorded	extensive	not recorded	+	not recorded	+	None	
X <i>Strep. viridans</i>	F 38	+	0	+	not recorded	+	extensive	0	0	not recorded	0	None	
XI Carcinoma	M 47	+	+	+	+	0	extensive	+	0	+	0	Right and Left	+
XII Carcinoma	F 43	+	+	+	+	not recorded	extensive	not recorded	0	not recorded	0	None	
XIII Cardiorenal Failure	F 37	+	+	+	+	+	extensive	0	0	not recorded	0	None	

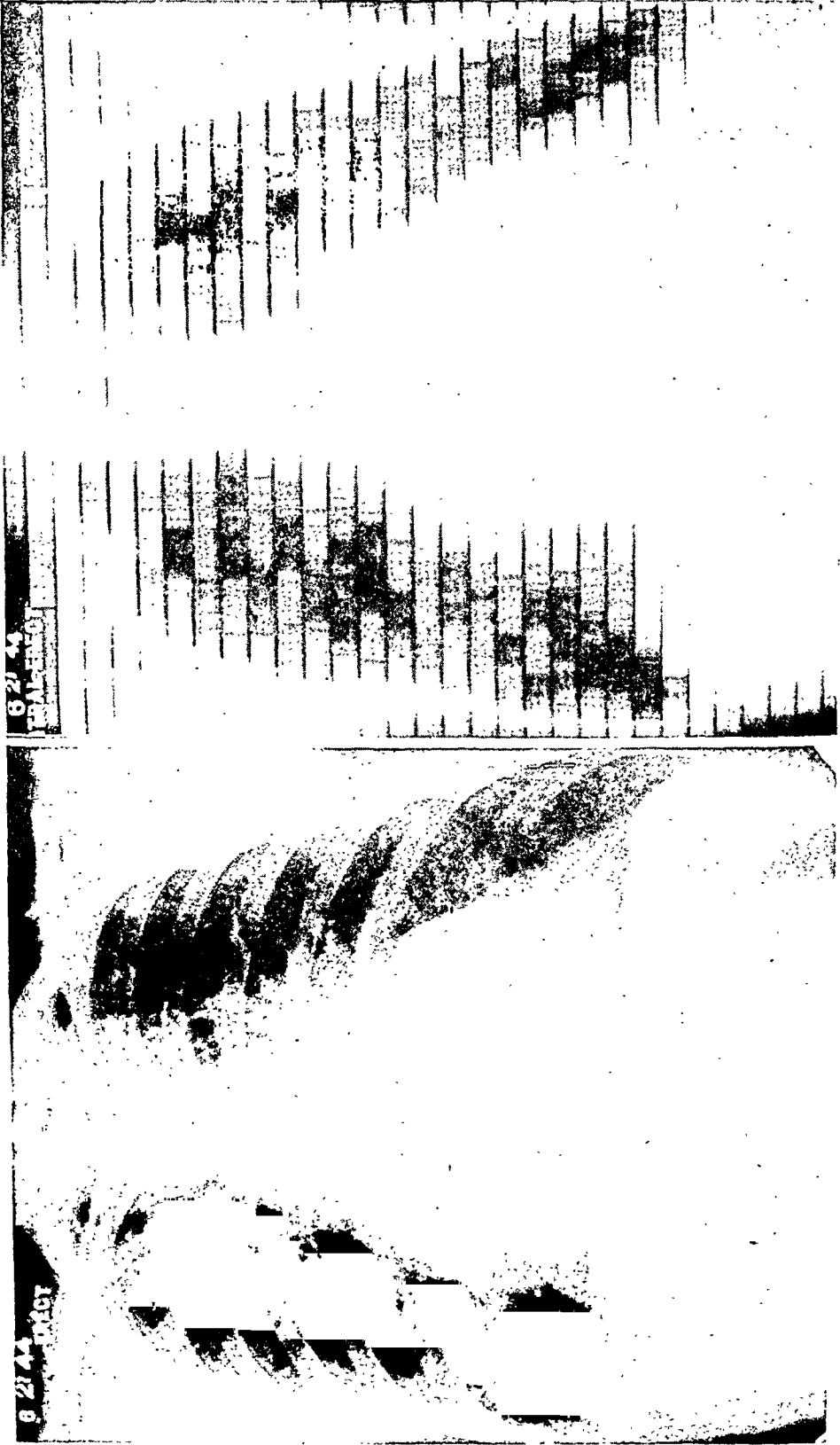


Fig. 3A. Case 11. Teleroentgenogram revealing a circular cardiac configuration. Fluoroscopic examination showed small amplitude of pulsations over the entire heart silhouette. No posterior deviation of the barium filled esophagus was present.

Fig. 3B. Roentgenkymogram showing small amplitude of pulsations of the heart and great vessels.

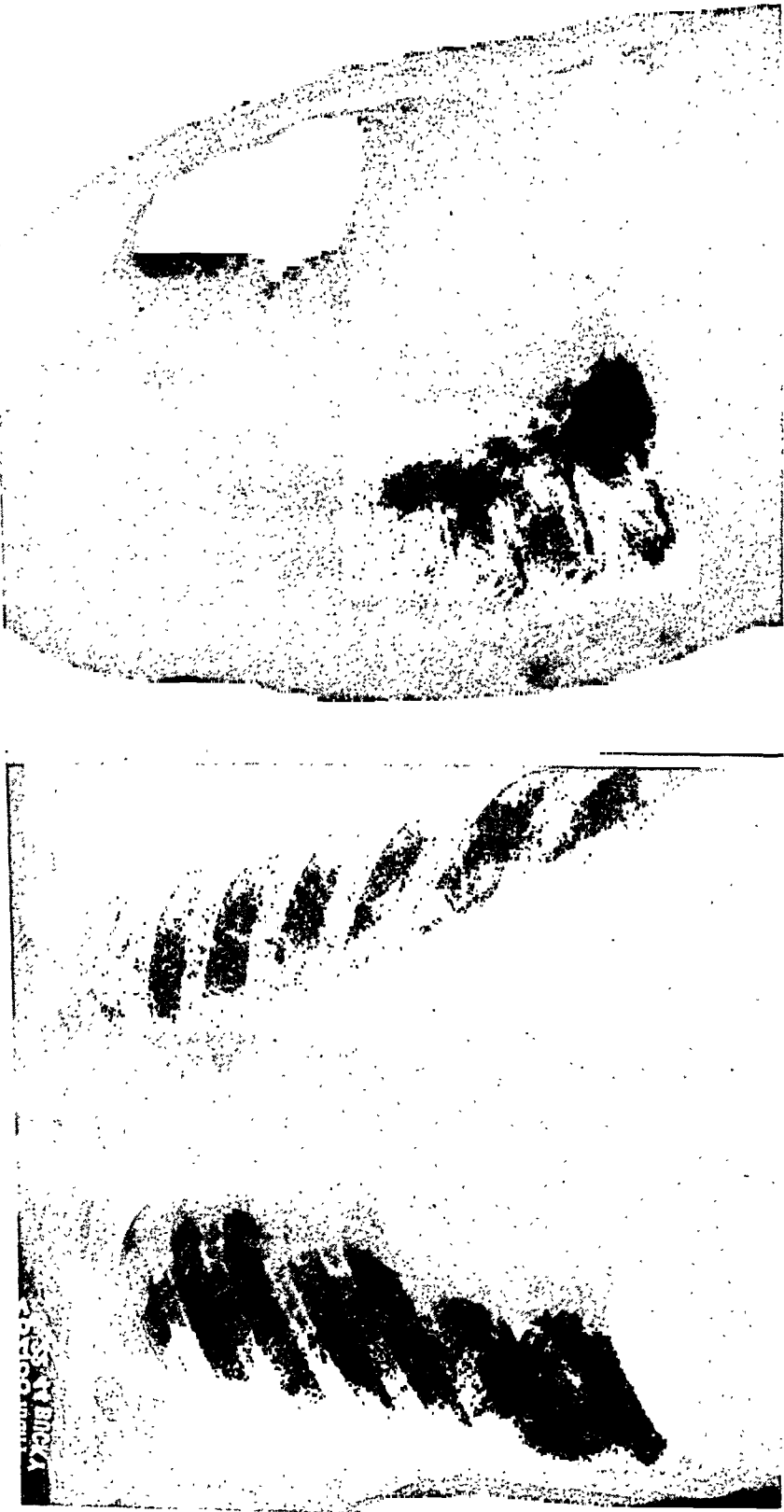


FIG. 3 C. Teleroentgenogram and left lateral roentgenogram of chest after the induction of hydropneumopericardium. Fluid levels may be seen in both projections within the pericardial sac.



pulsations of the heart borders. A diagnosis of pericardial effusion was made and confirmed by the induction of hydropneumopericardium. Considerable relief was obtained after the aspiration of 600 c.c. of serous fluid by the xiphoid approach. Four successive taps were performed for relief of symptoms, and pleural thoracentesis also became necessary. The fluid obtained on the last tap of the pericardial cavity was hemorrhagic. There was no response to treatment, and the patient died during the ninth week of hospitalization.

Autopsy revealed polyserositis with fluid in all the serous cavities and thickening of the pericardium and Glisson's capsule. Such findings are common in acute lupus erythematosus disseminata. The heart weighed 240 grams, and no gross endocardial or myocardial lesions were seen.

*Case 11.* G. L., male, 47 years old, was admitted to the Hospital during June 1944 because of a progressively severe cough, substernal pain and dyspnea. He had lost 30 pounds in the three months before admission. Orthopnea became marked and the neck veins were enormously distended.

Physical examination revealed a marked increase in the area of cardiac dullness extending from the left midaxillary line to the right midclavicular line, where the cardiohepatic angle was obliterated. The heart sounds were almost inaudible and the apex beat could not be identified. His pulse was paradoxical. There were signs of a moderate right pleural effusion. His liver was large and tender, extending down to the umbilicus. His venous pressure was 520 millimeters of water, the saccharine time was prolonged to 34 seconds, and the ether time to 18 seconds.

Teleroentgenographic examination of the chest showed a prominence of the left heart border, the cardiac contour assuming a water-bottle configuration. The cardiohepatic angle was not unusual. Fluoroscopic examination showed diminished pulsations of the heart and the great vessels. A small pleural effusion was present on the right side.

A diagnosis of pericardial effusion was made, and confirmed by the aspiration of 500 c.c. of serosanguinous fluid and the induction of hydropneumopericardium through the xiphoid route. There was considerable relief following the tap, and the venous pressure fell to 220 mm. of water. The paradoxical pulse disappeared. Pericardial aspirations were repeated three times, as much as 1200 c.c. being removed on one occasion. Thoracentesis became necessary as the right pleural effusion increased. The patient's course was progressively downhill. Short paroxysms of auricular flutter and auricular fibrillation appeared and subsided spontaneously. No relief was obtained from deep roentgen-ray therapy over the heart, and he died eight weeks after admission. Biopsy of a node removed from the left supraclavicular area revealed adenocarcinoma.

#### COMMENT

A review of the clinical observations in our series of 13 patients with large pericardial effusions revealed that all had distended neck veins and hepatic enlargement, indicative of increased venous pressure produced by the cardiac tamponade. Although all were dyspneic, only seven were orthopneic, indicating that pericardial effusion may exist in a patient able to lie in the recumbent position.

The most constant sign of pericardial effusion observed in all our patients was the broad area of absolute cardiac dullness extending over the anterior thoracic wall from the right midclavicular line to the left midaxillary line. This can usually be differentiated from the large area of relative dullness percussed over a large dilated or hypertrophied heart, which is

rarely flat beyond the right sternal border. Inferiorly, Traube's tympanitic space is obliterated because of the sagging due to the effusion. The lack of resonance on the right merges with that of the liver, producing an obtuse cardiohepatic angle (Rotch's sign). This is in contrast with the usual roentgenologic finding of an acute cardiohepatic angle. Hoover's sign, which is broadening of the base of the heart when percussed in the supine position and narrowing when percussed in the recumbent position, was not often elicited in our group of patients. Wolff<sup>6</sup> has emphasized the sharp transition from absolute dullness over the pericardial effusion to normal pulmonary resonance as an aid in diagnosis. This sign was present in some of our patients where no concomitant pleural effusion existed.

The apical impulse persisted in the six patients with enlarged rheumatic hearts, and was absent in three patients with normal hearts. The observation was not recorded in the others. Levine<sup>7</sup> has commented that the area of flatness often extends considerably to the left of the apical impulse, a sign which may be helpful if there is no left pleural effusion.

On auscultation diminution of the apical sounds with louder sounds at the base was noted in six of our patients. The pulmonic sound was often accentuated. In five patients a gallop rhythm was present. The pericardial friction rub usually was heard easily when the effusion was in its incipency, and as the fluid increased, the rub disappeared from the apex but often persisted at the base of the heart.

A paradoxical pulse was often noted with pericardial effusion and was present in five of the last six patients where it was especially sought. This aberration is accentuated by requesting the patient to hold his breath in deep inspiration when the pulse becomes perceptibly weaker or disappears. The paradoxical pulse may vanish after the pericardial fluid is withdrawn, and may return when the fluid reaccumulates. In this way it may serve as a guide for repeated aspirations.

Ewart's sign of left pulmonary compression by the pericardial effusion was found to be a diagnostic aid. All but one of our patients with inflammatory pericarditis, rheumatic, pyogenic and lupus erythematosus disseminata, showed this sign. However, neither of the patients with metastatic carcinomatous pericarditis with effusion showed this, even though one (case 11) had an enormous effusion. Our observation that Ewart's sign was seen only in inflammatory effusions confirmed the studies of Gevalt and Levine,<sup>8</sup> who maintained that a concomitant pneumonitis in the compressed lung tissue is necessary for the presence of the sign. In their series of patients with pericardial effusions only those of rheumatic origin exhibited a positive Ewart's sign.

The electrocardiogram was not very helpful. Two patients had auricular flutter and one had auricular fibrillation. Two had low T-waves and two others had low main ventricular complexes. The S-T elevation described in acute fibrinous pericarditis was not seen in our group.

Roentgenographic examinations revealed diffuse cardiac enlargement

in all our patients, but only six presented the so-called "water-bottle" configuration. The most reliable routine procedure was repeated observations for recession or progression in the size of the heart, which supplied positive information in 10 of our patients. Fluoroscopic observations were recorded in seven patients, and the difference in amplitude of pulsation over the heart margins and the great vessels was not considered definitely diagnostic. In the five patients with induced hydropneumopericardium the roentgenologic findings were conclusive. The fluid level within the pericardial sac and the waves caused by the heart action as seen fluoroscopically were unmistakable. An acute cardiohepatic angle was noted in 10 of our patients. It was noteworthy that the angle became almost perpendicular as the effusion receded, indicating that the acute angle is present only with large effusions.

### SUMMARY

The most reliable sign of pericardial effusion is the broad area of absolute cardiac dullness extending from the right midclavicular line to the left midaxillary line. Percussion flatness should be sought to the right of the sternal border in suspected cases of pericardial effusion. Ewart's sign may be elicited if the pericardial effusion is of inflammatory origin. Increased venous pressure is a constant finding, and a paradoxical pulse is frequently present.

The roentgenologic signs usually described as indicative of pericardial effusion may be difficult to evaluate, particularly in the presence of a concomitant pleural or pulmonary pathologic process. The artificial induction of hydropneumopericardium by the xiphoid approach is suggested as an additional roentgenologic diagnostic measure.

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## STUDIES ON SENSITIVITY OF DIPHTHERIA TO PENICILLIN \*

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IN August 1944 there was a sudden rise in the number of admissions of diphtheria cases to Letterman General Hospital from ships' hospitals and U. S. Army transports. Similar admissions after that date persisted in disconcerting numbers. Out of these cases about 12 per cent became ill the day of arrival at this hospital; about 26 per cent developed symptoms less than six days after arrival. About 62 per cent were ill while still aboard ship. The number of these cases and the number of diphtheria carriers developing posed quite a serious problem for a debarkation hospital, responsible for rapid sorting and transferring of overseas patients to appropriate hospitals. Consideration of means to improve the situation led to studies about to be reported:

Since the use of diphtheria antitoxin in appropriate doses, administered early, was giving such highly satisfactory results in control of the clinical, symptomatic diphtheria, this method of treatment was continued during the stage of subjective illness. In an attempt to reduce the duration of the carrier state, however, a plan of study, using penicillin, was considered. For the purposes of the experiment a carrier was considered to be a person who 10 days after onset of illness continued to have positive nasopharyngeal smears and cultures. A penicillin solution of 2,000 units per c.c. of 10 per cent glycerine in normal saline was adopted. This solution was nebulized by an ear, nose and throat unit, using air as a source of pressure in such an amount as would in 15 minutes nebulize  $2\frac{1}{2}$  c.c. of the penicillin solution or 5,000 units of penicillin sodium. Subsequently 100 per cent oxygen in such an amount as would displace  $2\frac{1}{2}$  c.c. of penicillin solution in 15 minutes was used with no appreciable change in the results because of the switch to 100 per cent oxygen. The first series of virulent diphtheria bacillus carriers treated with nebulized penicillin received four 15 minute treatments daily. The nebulized penicillin solution was dispensed through a Y-tube so that each nostril was fed the nebulized spray, the subject being directed during this time to inhale through the nose and to exhale through the mouth. Alternate similar cases as controls were treated identically but for the administration of inhaled penicillin. The results of this controlled series, more graphically demonstrated in table 1, indicated that penicillin so used was of no benefit in reducing the interval of carrier state, the cases

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treated with penicillin requiring on the average 29 days from the onset of illness to obtain three consecutive negative nasopharyngeal smears and cultures on alternate days; those not treated with penicillin required on the average 26 days to become similarly negative. Feeling then that possibly such solutions *inhaled* through the nose might leave certain blind spots in

TABLE I  
Penicillin Aerosol Group I  
(Nasally *inhaled*, orally *exhaled*)

Case No.	Date of Onset	Carrier	Case	Antitoxin	Aerosol Treated	Control	3 Neg. Cult.
1.	Dec. 22, 44		X	20,000 U I.M.	Jan. 29, 45		Jan. 31, 45
2.	Jan. 18, 45		X	20,000 U I.M.	Jan. 29, 45		Jan. 31, 45
3.	Jan. 5, 45		X	40,000 U I.M.	Jan. 29, 45		Feb. 2, 45
4.	Jan. 5, 45		X	40,000 U I.V.	Jan. 29, 45		Feb. 2, 45
5.	Dec. 31, 44		X	40,000 U I.V.	Jan. 29, 45		Feb. 4, 45
6.	Jan. 5, 45		X	40,000 U I.M.	Jan. 29, 45		Feb. 4, 45
7.	Jan. 1, 45		X	20,000 U I.M.	Jan. 29, 45		Feb. 4, 45
8.	Jan. 5, 45		X	20,000 U I.M.	Jan. 29, 45		Feb. 6, 45
9.	Feb. 1, 45	X		None	Feb. 8, 45		Feb. 23, 45
10.	Jan. 31, 45		X	40,000 U I.V.	Feb. 11, 45		Feb. 27, 45
11.	Jan. 28, 45		X	20,000 U I.M.	Feb. 12, 45		Mar. 11, 45
12.	Feb. 2, 45		X	20,000 U I.M.	Feb. 12, 45		Mar. 15, 45
13.	Feb. 9, 45	X		20,000 U I.M.	Feb. 13, 45		Mar. 13, 45
14.	Dec. 17, 44		X	18,000 U I.M.		X	Jan. 8, 45
15.	Feb. 23, 45			None		X	Feb. 28, 45
16.	Feb. 3, 45		X	60,000 U I.V.		X	Feb. 19, 45
17.	Feb. 6, 45	X		20,000 U I.M.		X	Feb. 21, 45
18.	Jan. 24, 45	X		20,000 U I.V.		X	Feb. 6, 45
19.	Jan. 19, 45		X	80,000 U I.V.		X	Feb. 21, 45
20.	Jan. 21, 45		X	40,000 U I.V.		X	Feb. 8, 45
21.	Jan. 25, 45		X	20,000 U I.M.		X	Feb. 21, 45
22.	Jan. 21, 45		X	10,000 U I.V.		X	Feb. 17, 45
23.	Feb. 22, 45	X		None		X	Mar. 19, 45
24.	Jan. 25, 45		X	20,000 U I.M.		X	Mar. 27, 45
25.	Jan. 22, 45		X	20,000 U I.M.		X	Mar. 13, 45
26.	Feb. 17, 45	X		20,000 U I.M.		X	

Average number of days from onset of illness to the obtaining of three negative q. 2 day smears and cultures: Penicillin-aerosol-treated cases—29 days; Controls—26 days.

the nasopharynx or on the turbinates, not contacted by the spray, which blind spots might be contacted should the mist be *exhaled* through the nose, a second series was run identical to the first with the exception that the nebulized penicillin was inhaled through the mouth and exhaled through the nose. Of this series, the penicillin treated cases required 33 days from date of onset of illness to become negative, those cases not treated with penicillin requiring 28 days. Having heard encouraging reports of the control of diphtheria carriers with the use of nebulized penicillin, using 100 per cent oxygen as the nebulizing gas, this gas was substituted for air in this second series in which the nebulized penicillin was inhaled through the mouth. Table 2 more graphically presents the results of this second and shorter series.

TABLE II  
Penicillin Aerosol Group II  
(Orally *inhaled*, nasally *exhaled*)

Case No.	Date of Onset	Carrier	Case	Antitoxin	Aerosol Treated	Control	3 Neg. Cult.
1.	Mar. 12, 45		X	Given	Mar. 27, 45		Apr. 28, 45
2.	Mar. 7, 45		X	"	Mar. 27, 45		Apr. 2, 45
3.	Mar. 8, 45		X	"	Mar. 27, 45		Apr. 10, 45
4.	Mar. 4, 45		X	"	Mar. 27, 45		Apr. 10, 45
5.	Apr. 21, 45		X	"	May 8, 45		May 24, 45
6.	Mar. 9, 45		X	"	Mar. 27, 45		Mar. 29, 45
7.	Mar. 23, 45		X	"		X	Apr. 18, 45
8.	Apr. 26, 45		X	"		X	May 18, 45
9.	Mar. 7, 45		X	"		X	Apr. 6, 45
10.	Apr. 24, 45		X	"		X	May 20, 45
11.	Mar. 9, 45		X	"		X	Mar. 25, 45
12.	Mar. 18, 45		X	"		X	Apr. 30, 45

Average number of days from onset of illness to the obtaining of three negative q. 2 day smears and cultures: Penicillin-aerosol-treated cases, 33 days; controls, 28 days.  
All had positive virulence tests.



FIG. 1.

Having understood that penicillin, especially if in solution, deteriorates on standing, it was felt that this deterioration might be due to oxidation. Should this be the case, then it would seem that 100 per cent oxygen as the nebulizing gas would be the least desirable agent. Accordingly, using

Heatly staphylococcus controls, the sensitivity of which is always in the range of 0.03 to 0.05 unit per c.c. of the penicillin solution, freshly prepared penicillin solution, and similar solutions through which 100 per cent oxygen had been passed for 15 minutes, were compared in vitro for their



FIG. 2.

bacteriostatic potency against virulent diphtheria. As can be seen in table 3, the sensitivity of the strains of *C. diphtheriae* studied to oxygenated or non-oxygenated penicillin is essentially the same. When the end point of a titration falls between 0.1 and 1.0 unit per c.c., the results are so reported. Experience has indicated that if organisms are resistant to more than 0.1

unit per c.c., there is little or no patient response. In other words, organisms, whose growth is inhibited by 0.01 to 0.09 unit per c.c. of penicillin, are considered sensitive. Those organisms that grow in higher concentrations of penicillin are considered insensitive.

Table 3 indicates also that there is a rather extreme variation in the sensitivity to standard solutions of penicillin in vitro, of virulent strains of *C. diphtheriae*, some strains in these in vitro tests seeming to be quite penicillin sensitive while others are penicillin tolerant.

To determine whether or not higher concentrations of penicillin solution nebulized into the nose would be locally irritating, solutions up to 50,000 units per c.c. were nebulized directly into the nasal chambers through the external nares with no evidence of increased irritation, the subjects reporting only an increase in the intensity of the odor of the material.

In an attempt to explain our failures in clearing up diphtheria carriers by the use of nebulized sprays of penicillin solution, it has occurred to us that possibly our solutions were too highly nebulized or that the concentration of our penicillin solutions was too low. Higher concentrations and a less minute droplet type of spray may possibly be more effective.

TABLE III  
In Vitro Penicillin Sensitivity of *C. diphtheriae* Strains

Case No.	Non-Oxygenated Penicillin Solution	Oxygenated Penicillin Solution
1.	between 0.1 and 1.0	between 0.1 and 1.0
2.	0.06	0.06
3.	0.1	0.1
4.	0.1	0.1
5.	0.05	0.06
6.	0.06	0.07
7.	0.04	0.03
8.	0.08	0.09
9.	0.08	0.09
10.	0.07	0.08
11.	0.1	0.1
12.	0.09	0.1
13.	between 0.1 and 1.0	between 0.1 and 1.0
14.	between 0.1 and 1.0	between 0.1 and 1.0
15.	0.02	0.03
16.	0.05	0.05
17.	0.09	0.09
18.	between 0.1 and 1.0	between 0.1 and 1.0
19.	0.03	0.03
20.	between 0.1 and 1.0	between 0.1 and 1.0
21.	between 0.1 and 1.0	between 0.1 and 1.0
22.	between 0.1 and 1.0	between 0.1 and 1.0
23.	between 0.1 and 1.0	between 0.1 and 1.0
24.	between 0.1 and 1.0	between 0.1 and 1.0
25.	0.03	0.04
26.	0.05	0.04
27.	0.05	0.05
28.	between 0.1 and 1.0	between 0.1 and 1.0
29.	0.05	0.06
30.	0.04	0.04
31.	between 0.1 and 1.0	between 0.1 and 1.0
32.	0.03	0.03



TABLE III—*Continued*

Case No.	Non-Oxygenated Penicillin Solution	Oxygenated Penicillin Solution
33.	0.04	0.05
34.	between 0.1 and 1.0	between 0.1 and 1.0
35.	between 0.1 and 1.0	between 0.1 and 1.0
36.	between 0.1 and 1.0	between 0.1 and 1.0
37.	between 0.1 and 1.0	between 0.1 and 1.0
38.	0.04	0.04
39.	0.02	0.02
40.	between 0.1 and 1.0	between 0.1 and 1.0
41.	0.09	0.09
42.	0.02	0.02
43.	0.03	0.03
44.	0.07	0.08
45.	0.04	0.04
46.	0.07	0.07
47.	0.03	0.04
48.	between 0.1 and 1.0	between 0.1 and 1.0
49.	0.02	0.03
50.	0.04	0.04
51.	0.07	0.07
52.	0.06	0.05
53.	0.06	0.07
54.	between 0.1 and 1.0	between 0.1 and 1.0
55.	0.08	0.08
56.	between 0.1 and 1.0	between 0.1 and 1.0
57.	0.1	0.1
58.	0.04	0.04
59.	between 0.1 and 1.0	between 0.1 and 1.0
60.	0.04	0.04
61.	0.04	0.05
62.	between 0.1 and 1.0	between 0.1 and 1.0
63.	between 0.1 and 1.0	between 0.1 and 1.0
64.	between 0.1 and 1.0	between 0.1 and 1.0

As can be seen from the above table, there is no difference in the sensitivity of the strains of *C. diphtheriae* studied when oxygenated or non-oxygenated penicillin is used, and some strains of *C. diphtheriae* are penicillin sensitive whereas others are penicillin tolerant.

*Note:* When the end point of a titration falls between 0.1 and 1.0 unit per c.c., the results are so reported, as experience has indicated that if organisms are resistant to more than 0.1 unit per c.c. there is little or no patient response. In other words, organisms whose growth is inhibited by 0.01 to 0.09 unit per c.c. of penicillin are considered sensitive, those organisms that grow in higher concentrations of penicillin are considered insensitive.

Heatly staphylococcus controls were used when each group of titrations was done. The sensitivity of the staphylococcus was always in the range of 0.03 to 0.05 unit per c.c.

### SUMMARY

1. Nasal inhalations and oral exhalations of 2,000 units of penicillin sodium per c.c. nebulized 2½ c.c. in a 15 minute interval four times a day failed to reduce the duration of the carrier state of virulent diphtheria bacilli.

2. Orally inhaled and nasally exhaled nebulized penicillin of the same concentration, using 100 per cent oxygen instead of air as the nebulizing gas, likewise failed to reduce the duration of carrier state.

3. The passing of 100 per cent oxygen gas through solutions of penicillin for 15 minutes did not reduce their potency or bacteriostatic property in vitro against virulent strains of diphtheria bacilli.

4. Nebulization of penicillin sodium, 50,000 units per c.c., into the nasal chamber was found non-irritating.

5. In vitro tests indicate that some strains of diphtheriae are penicillin sensitive whereas others are penicillin tolerant. Forty-one cultures of 64 cultures taken from 64 patients were penicillin sensitive. In percentage the frequency of sensitivity in this series was 64.0.

# PERIARTERITIS NODOSA: A CLINICOPATHOLOGICAL ANALYSIS OF SEVEN CASES\*

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## HISTORY

ALTHOUGH credit has been given to Kussmaul and Maier<sup>1</sup> for the original description of periarteritis nodosa in 1866, it is claimed that the disease was recognized as early as 1755 by Michaelis and Matani.<sup>2</sup> In 1810, Pelletan<sup>3</sup> reported a case in which "as many as 63 small aneurysms of various arteries were counted." In 1852, Rokitsansky<sup>4</sup> described the macroscopic lesions of the disease, and in 1877, Eppinger<sup>5</sup> confirmed the diagnosis by studying the microscopic sections of that case.

In a review of the literature in 1914,<sup>6</sup> a total of 38 cases of periarteritis nodosa was encountered. Of these, five were reported from the United States. Dickson<sup>7</sup> reported the first case in this country in 1907, and Longcope<sup>8</sup> the second in 1908. In 1928, Strong<sup>9</sup> collected 142 cases reported in the world's literature out of which 21 were recorded in journals published in the English language. By 1932, a total of 150 cases was reported in the world's literature,<sup>10</sup> and in 1933, 38 cases were collected from the English literature.<sup>11</sup> According to Harris et al.,<sup>12</sup> there were only 101 cases reported in English up to 1938, and only 300 in the world's literature; nevertheless, Baker<sup>13</sup> states that only a total of 200 reports was acceptable by 1939.

It is evident that periarteritis nodosa, a disease known for almost 200 years, has not received a great deal of attention until the last three decades. This is probably due to an increase in postmortem examinations and improvement in the clinical diagnosis of the condition. As evidenced by reports of Middleton and McCarter<sup>14</sup> (1935), Spiegel<sup>15</sup> (1936) and Harris et al.<sup>12</sup> (1939), some cases have been diagnosed before death.

## ETIOLOGY

The etiology of periarteritis nodosa is still in question. Chvostek and Weichselbaum<sup>16</sup> (1877) and Versé<sup>17</sup> (1907) suggested that the disease was caused by the *Treponema pallidum*. The consensus now is that a syphilitic process, if present in a case, is independent of the malady. Klotz's<sup>18</sup> (1917) idea that the disease was secondary to a streptococcic infection lacked convincing proof. The theory of parasitic etiology of Cameron and Laidlaw<sup>19</sup> (1936) had very little basis. Von Haun<sup>20</sup> (1920), and Harris

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and Friedrichs<sup>21</sup> (1922) suggested that the disease was of virus origin, but confirmation did not follow in spite of support from many followers. Ophüls<sup>22</sup> (1923), Friedburg and Gross<sup>23</sup> (1934) and Middleton and McCarter<sup>14</sup> (1935) claimed that the condition appeared secondary to rheumatic fever, and Vining<sup>24</sup> (1938) was of the opinion that a rheumatic infection sensitized and "prepared the way for the destructive virus of periarteritis nodosa." Harbitz<sup>25</sup> (1926) stated that generalized inflammation and necrosis of the focal type may be found in small arteries in conditions such as scarlet fever, diphtheria, carbon monoxide poisoning, influenza and suppurative processes. He believed that in spite of the great similarity, periarteritis nodosa is a clinical entity with specific etiology, in all probability a virus. In 1942, Baker<sup>13</sup> stated that "the generalized approved opinion is that periarteritis nodosa is a virus disease." Helpert and Trubek,<sup>26</sup> Krohulik et al.<sup>27</sup> (1935) and Lummis<sup>28</sup> (1936) favored vegetative endocarditis as an accompanying ailment in periarteritis nodosa, but there is not enough supporting evidence. In 1936, Cohen et al.<sup>29</sup> proposed that periarteritis nodosa was of allergic origin. They thought that the damage to the arteries was a severe allergic manifestation of irreversible character, and the pathologic changes occurring in the different organs were secondary to the arterial damage. They considered every patient suffering from allergy a potential victim of periarteritis nodosa. Rich<sup>30</sup> and Rich and Gregory<sup>31</sup> (1943) have submitted the most convincing proof that the disease may be of allergic origin. They have produced the typical lesions of periarteritis nodosa in rabbits sensitized with horse serum. The experiments clearly indicate that the disease may result from hypersensitiveness to an antigen, and suggest that the arterial changes may result from a reaction to antigenic substances of diversified nature.

### PATHOLOGY

The outstanding pathologic change consists of inflammatory lesions, usually focal, with normal intervening segments involving the middle sized and smaller arteries. In some instances, the lesion is confined to a portion of the circumference of the vessel, but as a rule the wall is completely affected. The pathologic change may be either local or general, at times occurring in only one vessel or organ. Cases in which the lesions have been limited to the nervous system have been described in great detail.<sup>32, 33</sup>

Arkin<sup>34</sup> has described four different stages for the lesions of periarteritis nodosa: (1) a degenerative stage, (2) a stage of acute inflammation, (3) a stage of granulation tissue formation, and (4) a healed stage.

In the early lesions the picture is that of an acute inflammation, characterized by serous exudate, fibrin formation, coagulation necrosis, cloudy swelling and hyaline degeneration of the media of middle sized and smaller arteries. Large numbers of polymorphonuclear neutrophils and eosinophiles are seen infiltrating the damaged areas of the vessels. Later, these

cells are replaced almost completely by lymphocytes, monocytes and plasma cells. The stage of repair is evidenced by moderate or marked fibroblastic proliferation. If healing occurs, there is marked scarring of the vessel wall resulting in narrowing of the lumen.

Ophüls<sup>22</sup> thought that the vessels were invaded through the lymphatics of the adventitia. The media is the first portion to be involved in the process, and later the inner coats are similarly affected. The outer coat is the last portion of the vessel to be damaged, and from this the process may spread into the perivascular tissues. This extension into the surrounding tissues, plus the sectional or focal damage of the arteries, may give rise to the periarterial nodule, which, when present in the periphery of the body, may serve as a good diagnostic aid.

The pathologic process may extend to larger arteries, arterioles and capillaries, and to the veins. The appearance of the lesions may vary tremendously even in the same sections of any artery, and in the same person depending upon the age of the lesion and the degree of the involvement. Thus, in one section, different stages of inflammation and repair may be seen.

Additional events following the vessel injury may be thrombosis, if the intima is involved, aneurysm formation, and rupture of the vessel with hemorrhage. Harris et al.<sup>12</sup> believe that aneurysms result from weakness at the site of the lesion due to poor fibroblastic proliferation. Thrombosis results in infarction of the area supplied by the affected vessel, but many of the thrombosed vessels may regain partial function if the clots are canalized.

It has been stated that no tissue is immune to the ravages of periarteritis nodosa. The organs involved in order of frequency are the kidneys, heart, liver, gastrointestinal tract, mesenteric arteries, muscles, spleen, lungs, and the peripheral and central nervous system.<sup>12, 35</sup> Secondary changes affecting the tissues are most frequently inflammation around the arteries, edema, atrophy, fibrosis, and necrosis or infarction, depending upon the abruptness of the occlusion of the involved vessels.

### CLINICAL PICTURE

The symptoms and physical findings are so protean in this disease that no true clinical pattern is suggested by either the history or the physical examination. The clinical manifestations, nevertheless, suggest disease in the most prominently involved organs or systems. For that reason, depending upon indefinite symptoms and signs, the disease has been clinically divided into six groups: the cerebral, neuromuscular, cardiac, cutaneous, gastrointestinal, and pulmonary groups.<sup>12, 35, 36, 37</sup>

Periarteritis nodosa is prominently a disease of adult life, but it has been reported among children, and is more common among males than females in a ratio of 3:1. The onset is acute in about half of the cases, and extremely insidious in the rest.

The disease is characterized by a picture of sepsis and toxemia with

temperatures ranging between 99 and 102° F. Remissions of the fever are common, and afebrile cases have been reported. Regardless of the organ or systems affected, a group of nonspecific symptoms and findings usually occurs. These are anorexia, weakness, loss of weight, tachycardia and leukocytosis.

Cardiac symptoms are very common since the coronary vessels are frequently involved. Anginal attacks and heart failure are frequent occurrences. Acute myocardial infarction, aneurysm formation in the coronary vessels as well as rupture with hemorrhage may occur. Pain in the right upper quadrant is, as a rule, due to chronic passive congestion of the liver, secondary to congestive heart failure.

Dyspnea and cough are frequent symptoms. They may be attributed to heart failure, but frequently may be due to lung injury from involvement of the pulmonary vessels. It must be remembered that dyspnea and cough are more frequently observed than edema resulting from congestive heart failure. According to Baker,<sup>13</sup> bronchitis and asthmatic attacks are the most prominent pulmonary manifestations.

Renal involvement, found in 80 per cent of the cases,<sup>13</sup> is characterized by albuminuria, cylindruria, hematuria, edema, nocturia, and hypertension. Renal hemorrhage may simulate stone, a tumor or essential hematuria. Some cases are indistinguishable from malignant hypertension.<sup>28, 38</sup> A rapid rise in blood pressure to high levels accompanied by fever and leukocytosis, in the presence of evident kidney damage, is very suggestive of periarteritis nodosa. The disease is, as a rule, of very short duration and terminates by uremia. Five out of 14 cases reported by Jones<sup>35</sup> died in terminal uremia. Keegan<sup>38</sup> believes that many cases of chronic nephritis may have their origin in mild periarteritis nodosa, since both periarteritis nodosa and arteriosclerotic nephropathy have been found at postmortem examination in some cases.

Gastrointestinal involvement is evidenced mainly by abdominal pain, nausea and vomiting. Symptoms may suggest a diagnosis of peptic ulcer, ulcerative colitis, acute appendicitis, or gall-bladder disease. Gastric ulceration, with hematemesis and perforation, is relatively frequent. Surgical operations based on mistaken diagnoses are not uncommon. Among these, nephrectomy, cholecystectomy and appendectomy have been reported.<sup>11, 15, 34, 39</sup> Felsen<sup>40</sup> believes that when the gastrointestinal tract is affected diagnosis can be made by rectosigmoidoscopic examination. He states that the most common findings are hemorrhage, thrombosis, and aneurysmal dilation of the vessels of the bowel wall. The liver may be the site of hemorrhage, or blood may flow into the peritoneal cavity. The symptoms referable to the liver may simulate common duct stone or cirrhosis.

Involvement of the nervous system is characterized by headache, muscular atrophy, especially of the intrinsic muscles of the hands and feet, sensory changes consisting of anesthetics and paresthesias, visual disturbances, convulsions, and vertigo. An illustrative case describing the sensory changes

accompanying the disease has been reported by Fitz et al.<sup>41</sup> Reports have been made of periarteritis nodosa of the retinal vessels<sup>26</sup> and the ophthalmoscopic picture described.<sup>42, 43</sup>

Skin lesions are not very common and quite varied. They may appear in the form of urticaria, nodules, ulcerations, purpuric manifestations, ecchymosis and gangrene. Since cases of purpura hemorrhagica accompanying periarteritis nodosa have been reported,<sup>44, 35</sup> the differentiation from Henoch's or Schönlein's purpura is sometimes difficult. Pain and swelling of the joints are of relatively common occurrence,<sup>35</sup> and this further complicates the differential diagnosis of the disease.

### LABORATORY DIAGNOSIS

Diagnosis can be made by muscle biopsy in a minority of the cases. If the disease is localized in some internal organ, this procedure is valueless.

Blood studies reveal an anemia of moderate severity in the majority of cases. Leukocytosis is one of the most constant findings ranging between 10,000 and 60,000 per cu. mm. of blood. Eosinophilia is inconstant, found only in about 20 per cent of the cases. Nevertheless, if eosinophilia is found in conjunction with nodules in the skin, an antemortem diagnosis is possible. It has been demonstrated that in cases of complications the eosinophilia is decreased and there is a shift to the left with a marked increase in the neutrophiles.<sup>12</sup>

### TREATMENT

There is no adequate nor specific treatment for the disease. Symptomatic management is the only recommendation. To prevent or treat serious complications, the sulfonamides have been found to help. Kerr<sup>45</sup> has suggested the use of vitamin C, but it has been of no help. Neoarsphenamine is valueless.<sup>46, 47</sup>

### PROGNOSIS

Only a few patients were known to have recovered from the disease up to 1939,<sup>12</sup> and long survival is rare. Fitz et al.<sup>41</sup> reported two cases that lived for eight and six years respectively after the onset of the disease, and mention is made of one that lived 12 years.<sup>48</sup> A few patients have lived four years or more.<sup>49, 50</sup>

### CASE REPORTS

*Case 1.* G. S., a 27 year old white male, was admitted to the Louisville General Hospital on February 15, 1943 asserting that he had been feeling quite well except for occasional headaches until five days previously, when he had a convulsive seizure while walking down the street. He fell, but did not completely lose consciousness. He was restless and confused for the next two days, and about four days after the convulsion he had a transient difficulty in talking. On the fifth day after onset, he was again taken with a convulsive seizure and was admitted to the ward for observation. Past history and family history were not remarkable.

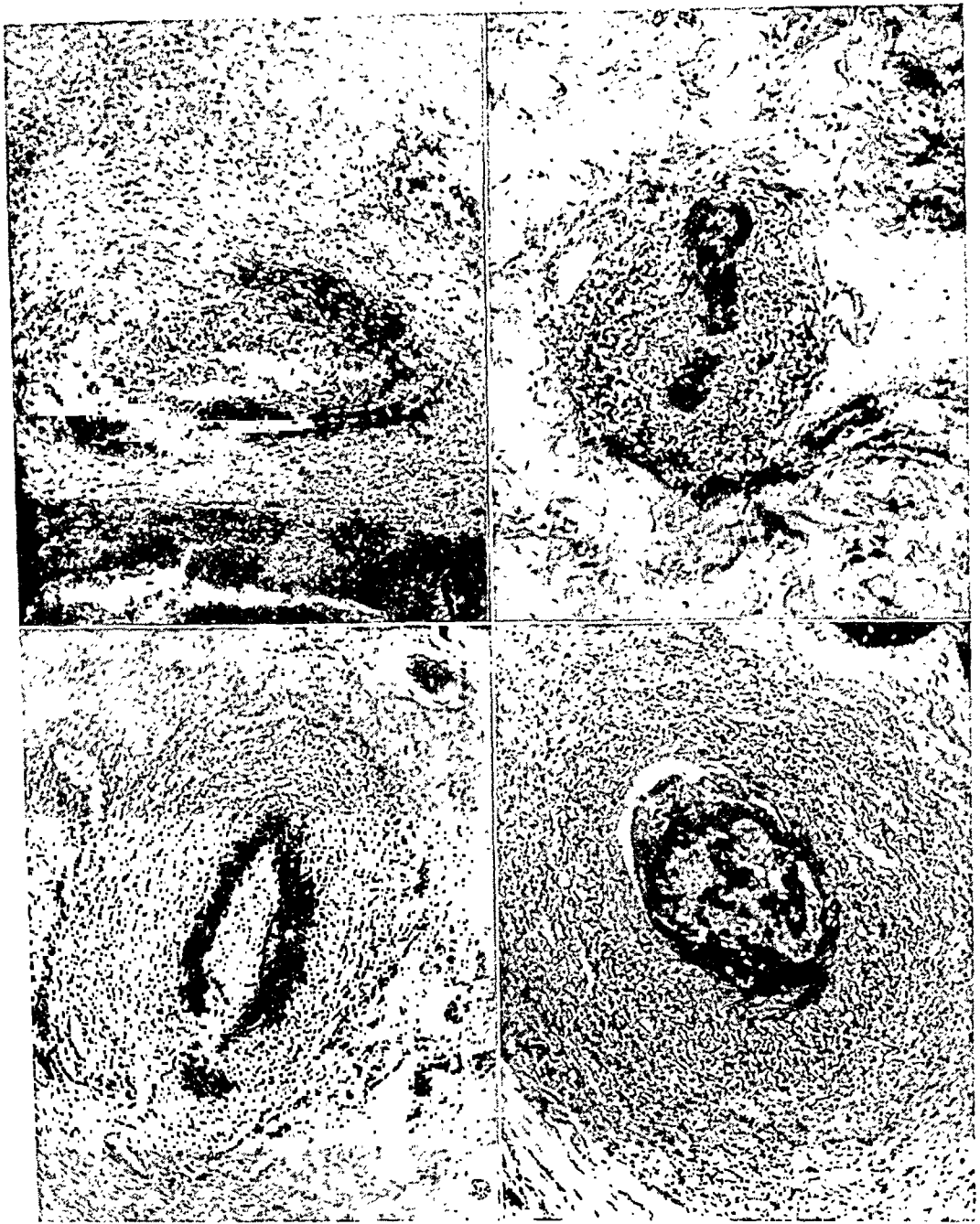


FIG. 1. *Case 1.* Periarteritis nodosa in a medium sized artery of the meninges. The entire wall is damaged, fibrin has formed in the intima. There is no thrombosis.

FIG. 2. *Case 2.* Periarteritis nodosa in small artery of the stomach submucosa.

FIG. 3. *Case 2.* Periarteritis nodosa with thrombosis in a small artery in the appendix submucosa.

FIG. 4. *Case 2.* Periarteritis nodosa with thrombosis in a small artery in the ileum submucosa.



On physical examination his pulse, temperature, respiration and blood pressure were within normal limits. Except for hyperactivity of knee jerks, biceps and triceps reflexes, and a positive Babinski on the left side, his physical examination was essentially negative. The serologic test for syphilis in the blood was doubtful, but the spinal fluid, which showed normal dynamics, was negative for syphilis. Electroencephalographic studies suggested a tumor mass or lesion on the right frontal lobe. An air encephalogram was interpreted as showing a large mass in the right posterior temporal area, possibly neoplastic.

On January 13, 1943, under local anesthesia, a craniotomy was performed. The brain was found to be under increased tension with practical obliteration of the sulci and gyri. A tumor mass was removed from the right frontal region.

He had an uneventful postoperative course except for headaches during the first few days and transient facial weakness. At the time of this report the patient had been observed for a year and seemed to be in good health.

Pathology: Grossly, the specimen consisted of soft, yellow colored brain tissue weighing about 100 gm. which did not appear to be neoplastic.

Microscopic examination showed large areas of coagulation necrosis involving the meninges, the cortex and some of the white substance, which was being organized by vascular granulation tissue. The medium and small sized arteries and veins were severely damaged. In the most acute lesions, coagulation necrosis of the media with infiltration by neutrophils, and to a lesser degree by monocytes, lymphocytes and occasional eosinophiles was observed. There was marked perivascular infiltration with the same types of cells. In the older lesions, there was marked proliferation of connective tissue in the media and especially the intima, the hyperplasia resulting in some cases in almost complete occlusion. No totally healed lesions were seen. Thrombosis was variable from none to complete, and organization with recanalization was seen in various stages. Preoperative hemorrhage was very slight. It was apparent that the necrosis was secondary to the inflammatory lesions of the arteries.

Diagnosis: Periarteritis nodosa.

*Case 2.* A 20 year old colored male was admitted to the Louisville General Hospital on April 28, 1943 stating that 16 days previous to admission he had been taken suddenly with pain in the back and in the epigastric region, chills, fever, burning on urination, and a severe diarrhea. A few days later he developed soreness and pain in the neck. He had lost approximately 10 to 15 pounds during his short illness and was very weak. He had nausea without vomiting. The past history was negative except for gonorrhea two months previous to admission.

Physical examination revealed a well developed and well nourished negro with a temperature of 100.2° F., pulse 108, respirations 24 and blood pressure of 144 mm. Hg systolic and 80 mm. diastolic. He had epigastric and costovertebral tenderness, moderate oral sepsis, and hyperactive reflexes throughout.

Urinalysis showed a normal specific gravity, but large amounts of albumin and numerous hyaline and coarsely granular casts, as well as 25-30 red blood cells per high power field. Roentgenographic studies showed a penetrating ulcer over the lesser curvature of the pyloric antrum. The erythrocyte count was 4.15 millions, with 70 per cent hemoglobin; and the white blood cell count 17,160 with a differential of 77 neutrophils, 22 lymphocytes and 1 monocyte. Since the fever did not recede, the patient was given sulfathiazole in addition to an ulcer régime which had been instituted previously, but this was to no avail.

Twenty-four days after admission his blood pressure went up to 170 mm. Hg systolic and 114 mm. diastolic. The patient did not improve and was subjected to an exploratory laparotomy. The surgeon could not find an ulcer, but he biopsied the stomach and removed the appendix.

Eight days postoperatively he had a convulsion accompanied by involuntary defecation and two days later he died after a second convulsion.

Pathology: Appendix and biopsy from the stomach wall: Grossly the tissue submitted for examination consisted of a portion from the stomach wall and the appendix. Both appeared to be normal.

Microscopically, in the small arteries of the muscularis of the stomach, there was hyalin necrosis of the media with perivascular infiltration mainly of lymphocytes,



FIG. 5. Case 3. Periarteritis nodosa in the basilar artery. The media, central part, is necrotic. Part of the swollen internal elastic membrane remains. Organizing thrombus below.

FIG. 6. Case 4. Periarteritis nodosa of right coronary artery.

a few neutrophils and monocytes. There was hyperplasia of the media and intima of some vessels, but thrombosis had not occurred. In the appendix hyalin necrosis was observed involving all the coats of the small and medium sized arteries. There was a thick infiltration of lymphocytes, monocytes and neutrophils, accompanied

by complete thrombosis of some vessels. There was very little repair, but some thickening of the intima and adventitia had occurred. In the serosa there was scarring, with perivascular infiltration chiefly by neutrophiles. There were several superficial erosions of the mucosa with scarring and leukocytic infiltration of the submucosa.

Diagnosis: Periarteritis nodosa of stomach and appendix.

Necropsy: The peritoneal cavity contained about 1000 c.c. of clear straw-colored fluid and there were adhesions of the omentum to the abdominal wall at the site of the surgical incision. There were adhesions between the gall-bladder and the visceral peritoneum and the liver, which was enlarged and attached to the parietal peritoneum. About 50 c.c. of clear fluid were found in each pleural cavity, and the left lung presented adhesions posteriorly, laterally and inferiorly. The heart was moderately hypertrophied, weighing 390 gm. There were nodules in the course of the coronary arteries, and small petechial hemorrhages as well as "soldier's plaques" were observed in the external surface of the heart. The right lung weighed 270 gm. and the left 250. Some of the peribronchial nodes had necrotic centers and the mesenteric nodes were large and soft. The intestinal mucosa had petechial and ecchymotic hemorrhages. The liver weighed 1,780 gm. and had a few yellowish infarcted areas. The right kidney weighed 260 gm., the left 200. There were multiple infarcts of a whitish yellow color in each. On the cut surfaces, thrombosis of the middle sized vessels was evident. The brain weighed 1,340 gm., and was found to be essentially normal.

Microscopically, a great number of the middle sized and smaller arteries, as well as some veins of the kidneys, stomach, ileum, pancreas and heart were markedly damaged. A few of the lesions consisted of old scars with very little leukocytic infiltration and canalized thrombi filling the lumen of the vessels. In the most recent foci, hyalin necrosis involved the entire wall or a segment of the wall with a peripheral zone of leukocytic infiltration. Organized and recent thrombi were observed on these vessels. Other lesions were in various stages between these two extremes. The disease was apparently progressive. In no instance was there evidence of the lesion beginning in the adventitia and extending into the media. Infarcts in the stage of coagulation necrosis were seen in the kidneys. No myocardial infarcts were observed.

Diagnosis: Periarteritis nodosa of kidneys, stomach, appendix, ileum, pancreas and heart.

*Case 3.* A 50 year old colored man was admitted to the Louisville General Hospital in a state of coma and in extremis. Physical examination revealed a temperature of 102° F., a pulse of 140, and respirations of 60 per minute. His blood pressure was 100 mm. Hg systolic and 85 mm. diastolic. He was deeply cyanotic and his skin was extremely cold. Fine râles were heard over the left lung base. The extremities were flaccid, but the patellar, biceps and triceps reflexes were hyperactive on the right side. There was absence of the abdominal, cremasteric and plantar reflexes bilaterally. A lumbar tap performed on admission revealed a grossly bloody fluid, under a pressure of 220 mm. of water. Blood studies revealed 4.8 million red blood cells per cu. mm., with 80 per cent hemoglobin and 16,700 white blood cells with 60 per cent neutrophiles, 33 per cent lymphocytes and 7 per cent monocytes. His blood Kahn reaction was doubtful and a urinalysis showed nothing but a trace of albumin and a few red blood cells per high power field. An electrocardiogram revealed defective intraventricular conduction (left bundle branch block) and myocardial damage. A roentgenogram of the chest demonstrated enlargement of the heart involving chiefly the left ventricle, very little widening of the aorta, and marked cloudiness of both lungs probably due to passive congestion. The patient did not respond to any kind of medication. His temperature oscillated between 102° and

103° F., his pulse between 90 and 130 per minute, and his respirations between 60 and 70. He died 24 hours after admission.

Necropsy: The heart weighed 420 gm., the left ventricular wall measuring 28 mm. in thickness, and had a few fine, gray scars. The aorta was only slightly dilated and showed raised longitudinal intimal ridges just distal to the aortic valve. The



FIG. 7. *Case 4.* Periarteritis nodosa in right coronary artery. Field is selected from figure 6.

FIG. 8. *Case 4.* Periarteritis nodosa in small artery of uterus.

coronary vessels appeared slightly sclerotic. The right lung weighed 630 gm., and was non-crepitant and purplish in color. The surface appeared rather granular. The left lung weighed 360 gm., and presented moderate congestion in the lower lobe. The liver weighed 2,160 gm. Both kidneys were moderately congested, the right weighing 150 and the left 160 gm. Poor demarcation between the cortex and the

medulla was observed. There was hemorrhage into the right adrenal gland. The brain was swollen and the convolutions were somewhat flattened from pressure. Over the base was a layer of blood, 8. mm. in thickness in the subarachnoid space. On dissecting away the blood a thickened enlargement of the basilar artery was found just proximal to its bifurcation into the posterior cerebral arteries. This enlargement was approximately 3 by 6 mm., and it had ruptured through its inferior surface. No other lesions of the vessels were noted.

Microscopy: The wall of the basilar artery was well preserved save at the site of rupture where there was necrosis, chiefly of the liquefaction, but partly of the coagulation type. There was a dense leukocytic infiltration; the bulk of which was neutrophilic. The lesion appeared to have been a rapidly progressing inflammation which weakened the wall to such an extent that it ruptured. The lumen of the artery was almost completely filled by recently formed but well differentiated connective tissue, evidently an organized thrombus several months old. One giant cell was seen in the necrotic tissue. Latent syphilitic reactions were seen in the aorta, adrenal gland, brain and testicle. These consisted of small lymphocytic infiltrations with slight scarring, focal atrophy of the testicle, and vascularization of the media of the aorta.

Diagnosis: Periarteritis nodosa of the basilar artery with rupture.

*Case 4.\** A. K. O., a nine month old white female was admitted to the Children's Free Hospital on July 14, 1943, with the information that she had suddenly been taken ill with a sore throat and fever about two weeks previously. She was taken to a physician who prescribed sulfathiazole in adequate doses. Five days later, this drug was discontinued because of the appearance of a rash. By that time the throat had improved, but a few days later her fever intensified and a urinalysis revealed pus. She was then treated symptomatically and improved. On the assumption that the rash was allergic in origin, the patient received large doses of ephedrine, but this was of no avail. The rash was worse at night, disappearing almost completely in the morning. The patient developed edema of the face and lower extremities several days before admission. On physical examination she was found to have a pulse rate of 110 and respirations of 30 per minute. Her temperature was 101° F., and the blood pressure 130 mm. Hg systolic and 80 mm. diastolic. The patient was very ill and presented some edema of the eyelids, a reddened throat bathed in exudate, and a red macular rash covering the whole body. The examination was otherwise negative.

The urine was normal, the usual agglutination tests and blood cultures were negative. The white blood cell count averaged 18,500 per cu. mm. with a differential count of 55 per cent neutrophils including 15 nonsegmented forms, 1 per cent metamyelocytes and myelocytes, 2 per cent eosinophiles, 38 per cent lymphocytes and 3 per cent monocytes. She had a mild secondary anemia. Roentgenogram of the chest revealed infiltration of the right lung consistent with a chronic inflammatory process.

After her evening feeding on the second day of hospitalization, she was suddenly taken with severe cyanosis and dyspnea and died within a few seconds.

Necropsy: The pericardial cavity was somewhat bulging and contained 40 c.c. of straw-colored fluid. The heart was enlarged, the epicardium containing some petechiae. The left coronary artery and anterior descending branch were firm and dilated for 2½ cm. of their course, the dilation starting about 1 cm. from the coronary orifices. The interior diameter of the vessels was about 3 mm., and when opened they contained a laminated blood clot. The right coronary artery was identically affected, but did not contain a blood clot. The right common iliac artery had a dilatation about 2½ cm. in length and was markedly damaged. The liver was enlarged moderately and grossly showed signs of acute degeneration.

\* Reported elsewhere.<sup>51</sup>

Microscopically, lesions were found in the right common iliac artery, coronary arteries and in the medium-sized and small arteries of the uterus. The damage was characterized by necrosis of the entire vessel wall, thrombosis, leukocytic infiltration, and beginning organization. The necrosis was of the coagulation type with rapid

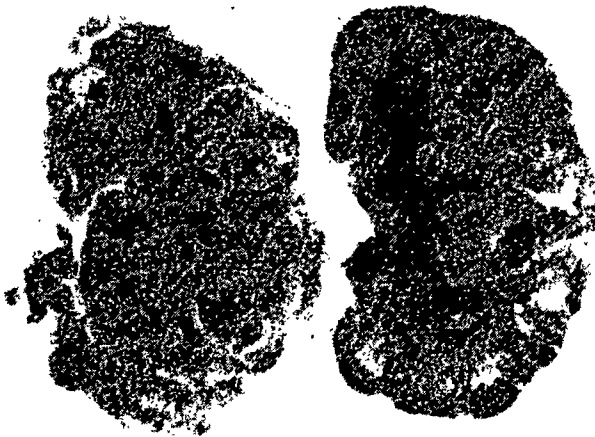


FIG. 9. *Case 4.* Periarthritis nodosa of right iliac artery.

FIG. 10. *Case 5.* Multiple infarcts of kidney in periarthritis nodosa.

liquefaction. The infiltration consisted chiefly of neutrophils, a moderate number of monocytes, and a few lymphocytes and eosinophils. The thrombi were all recent, some of them occluding the arteries. Organization had just begun. The lungs were edematous and congested and the liver parenchyma swollen.

Diagnosis: Periarthritis nodosa of the coronary, uterine and right common iliac arteries.

*Case 5.* L. T., a 39 year old white male, was admitted to the Louisville General Hospital on March 1, 1943, complaining that he had been vomiting for two weeks and had had fever for two months. A month previous to admission his private physician told him he had renal disease. For some six weeks before admission he had complained of weakness and bouts of shooting pains in the legs and thighs and more recently of numbness and tingling of the fingertips of the right hand. In six weeks he had lost 50 pounds in weight, and during the last two weeks he had had a hacking cough. Partial paralysis of the feet and ankles had appeared during these two weeks, and he had suffered from headache at the same time. He had had typhoid vaccine some nine weeks previously.

On examination the temperature was 101° F., pulse 100, and respirations 26 per minute. The blood pressure was 156 mm. Hg systolic and 88 mm. diastolic. He was markedly dehydrated; the right pupil was dilated and fixed, and there were signs of right-sided early bronchopneumonia. He had a loss of strength of his lower extremities, had no vibratory sense bilaterally up to the iliac crests, and had lost the sense of light touch as well as pain and temperature to a level above the knees. The patient was euphoric. On the seventh day of hospitalization he had a sudden attack of dyspnea with a rapid heart and gallop rhythm, pedal edema and evidence of pulmonary congestion. He had similar episodes repeatedly until death on his eighteenth day of hospitalization. On admission the white blood cell count was 24,100 with 73 mature neutrophils and 10 nonsegmented cells, 3 eosinophils, 8 lymphocytes and 6 monocytes. He had a mild secondary anemia. The cephalin cholesterol flocculation test was strongly positive, and the sedimentation rate markedly accelerated. The blood serologic test was negative, no growth was evident on 7 blood cultures, and sputum examinations and guinea pig inoculation were negative for tuberculosis. Urine had a specific gravity of 1.020 and was negative except for a fairly large quantity of albumin. The spinal fluid was negative and roentgenogram of the chest showed some hypertrophy of the heart and pulmonary congestion. Electrocardiographic studies demonstrated myocardial damage. The fever curve during hospitalization oscillated between 98 and 102° F., with a rise to 103° just before death.

*Necropsy:* The liver was enlarged, weighing 2,030 gm. There was an effusion of around 500 c.c. in the right pleural cavity. The heart weighed 410 gm. The left ventricle wall measured 18 mm. A few petechiae were seen on the smooth surface of the parietal pericardium, and a fibrinous exudate on the epicardium. There were two areas of scarring, 2 cm. in diameter over the right ventricle, anteriorly. There were multiple petechiae in the epicardium, mainly in the posterior aspect of the heart, especially in the region of the atrioventricular sulcus. Four depressed areas, the largest 10 by 5 mm., were observed over the surface of the myocardium. Small yellowish areas were noted beneath endocardial surface of the left ventricle, the largest one being beneath the medial cusp of the mitral valve involving the papillary muscle and measuring 1.5 by .5 cm.

Infarcts of different ages were found throughout the myocardium of the right ventricle. The right lung weighed 1,430 gm. and a fibrinous exudate covered its surface. Massive bronchopneumonia with edema was observed. The left lung weighed 1,150 gm., and it was similarly affected. The spleen weighed 130 gm., was adherent to the diaphragm, omentum and colon, and had four infarcts. The pancreas had multiple small infarcts. The right kidney weighed 160 gm., the left 150. Both organs had multiple infarcts including most of their surfaces. On sectioning, there were multiple bulbous dilatations of the vessels averaging 3 mm. in diameter, which, when cut open, contained dark clots. The brain weighed 1,480 gm., and the meninges were scarred along the course of the vessels.

Microscopically, in the heart muscle were numerous infarcts varying in age. The most recent ones consisted of areas of coagulation necrosis, the older ones being in various stages of organization, whereas the oldest were only hyalinized scars. In

the small branches of the coronary artery there were local sections of hyalinized scars some of which were organized thrombi. In other arteries the thrombosis was recent. There was very little leukocytic infiltration in and about the vessels. Similar infarcts and arterial lesions were found in the spleen, kidneys, ileum, colon, pancreas and



FIG. 11. *Case 5.* Periarteritis nodosa in arcuate artery of kidney. Mural thrombus below.

FIG. 12. *Case 6.* Hemopericardium, caused by rupture of anterior descending coronary artery, aneurysm, due to periarteritis nodosa.



liver. The most active reaction was in a middle-sized artery at the kidney hilus, where an infiltration by lymphocytes and neutrophiles had occurred in and about the artery. In the other organs, many of the thrombi were quite recent and not accompanied by leukocytic infiltration or focal necrosis of the arterial wall. The lungs were in the late stages of bronchopneumonia.

Diagnosis: Periarteritis nodosa of the coronary, mesenteric, renal, splenic, hepatic and pancreatic vessels with infarction.

Case 6.\* N. C., a five year old white female, was admitted to the Louisville General Hospital on February 5, 1943 complaining of a sore throat since January 31, 1943 accompanied by fever at times reaching levels of 105° F. She complained of pain in the legs and had vomited frequently since the onset of the illness. Three days prior to admission she developed a rash on the hands, feet and genitalia which later became generalized. Because of the vomiting, she had been unable to eat much and was quite weak. She had been immunized against diphtheria with toxoid and had been vaccinated against smallpox when she was six months old. She had had measles, whooping cough and Flexner type of dysentery between her first and fourth years of age, but during her fifth year she had had no illnesses with the exception of occasional sore throats. There was a doubtful history of tuberculosis in her mother.

She had a pulse of 120, respirations of 32 per minute, and a temperature of 103.4° F. She was in a semilethargic state. There was injection of the conjunctivae, and infection of the right ear drum without bulging. The tonsils were hypertrophied and the throat was injected. The skin had an atypical scarlatiniform rash on the feet, hands, genitalia and forehead. There were signs of early bronchopneumonia. Reflexes were hypoactive throughout. The white blood cell count was 22,000 per cu. mm. with 58 per cent segmented, 2 per cent nonsegmented, 38 per cent lymphocytes, 1 per cent eosinophiles and 1 per cent monocytes. The urine was negative, as were throat and blood cultures. The Schick test was positive; the tuberculin test was negative. The patient was given sulfathiazole in adequate doses and the temperature returned to normal in three days; nevertheless, it soon went up to 99.2° F. She appeared very much better, but on February 9, 1943 (four days after admission) she was suddenly taken with severe dyspnea and cyanosis and died within a few seconds.

Necropsy: The liver was moderately enlarged, weighing 920 gm. It was dark in color, and localized areas of scarring of the capsule were observed. The pericardial cavity was distended and bluish in color. When it was opened 75 c.c. of reddish serum welled out. A blood clot was found surrounding the heart. Upon further dissection it was observed that at the junction of the left coronary, circumflex and anterior descending arteries there was an aneurysm about 8 mm. in diameter and 2.5 cm. long extending down the anterior descending branch. The left coronary supplied the sac with blood which flowed out after a detour in the aneurysmal sac into the circumflex and descending branches. The sac had a thin anterior wall consisting of epicardium and granulation tissue only. It had ruptured at a point comparable to the origin of the anterior descending artery. The lining was smooth, but just to the right of the anterior descending artery's inlet there was a recently formed blood clot 3 mm. thick, 7 mm. long and 3 mm. wide. The heart weighed 110 gm. The lungs showed some areas of bronchopneumonic consolidation. The brain was moderately swollen and its vessels congested.

Microscopically, the wall of the aneurysm consisted chiefly of slightly scarred epicardium, but in some sections a small portion of the arterial wall remained. In the wall of the vessel and the surrounding fat, there was a dense infiltrate consisting of a very few neutrophiles, about an equal mixture of monocytes, plasma cells and lymphocytes, and a moderate number of eosinophiles. Clinging to the lining was a

\* Reported elsewhere.<sup>51</sup>

thrombus into which a few fibroblasts had grown. In and about the wall of some of the veins and smaller arteries of the heart muscle there were lesions of a similar type, but much less severe. Here the infiltrating cells were mainly plasma cells and lymphocytes. The lungs were edematous and in local areas leukocytes had filled the air sacs and small bronchioles.



FIG. 13. Case 6. Periarteritis nodosa of anterior descending coronary artery.

FIG. 14. Case 7. Periarteritis nodosa of medium sized coronary artery, with organizing thrombus.

Diagnosis: Periarteritis nodosa of the coronary arteries and veins with aneurysmal formation, rupture and cardiac tamponade.

Case 7. F. C. C., a 25 year old colored male, was admitted to the Louisville General Hospital on April 11, 1944, stating that a month previously he had been taken

with severe pain in the back "around the kidneys" and a "crushing" pain in the testicles. These symptoms were accompanied by pain and soreness in the right elbow, shoulder and right knee joints, as well as in the calf muscles. For the three months preceding admission he had been suffering from stabbing pains in the precordium and dyspnea on exertion. Four days previous to admission, he had been taken with pain in the epigastric region and lower abdomen accompanied by nausea; the other symptoms intensified, and he was forced to seek medical attention. He had had dysuria and nocturia for the preceding five days, and had lost six pounds during the period of abdominal symptoms.

In 1939 he had acquired gonorrhea and syphilis, but claimed proper treatment. For 16 years he had had periodic spells of "sick headaches" accompanied by nausea and vomiting which forced him to go to bed every two to three months. His family history was negative.

On examination he appeared well nourished and well developed, with a blood pressure of 110 mm. Hg systolic and 70 mm. diastolic, pulse of 76, respirations of 24 per minute, and a temperature of 99° F. He had inguinal and axillary adenopathy, a reddish throat, hypertrophic tonsils, abdominal gaseous distention, and tenderness in the epigastric region and lower abdomen. The prostate was enlarged and tender. The abdominal reflexes were absent and all the other deep reflexes were hypoactive. The right testicle was enlarged and tender.

Examination of blood revealed a red cell count of 3.5 millions and 11.5 gm. of hemoglobin; 26,700 white blood cells with 62 neutrophils, 2 nonsegmented, 18 lymphocytes, 16 eosinophiles and 2 monocytes. Five additional counts presented a similar picture with eosinophiles varying from 6 to 16 per cent. The urine was normal except for small amounts of albumin and a few granular casts. Roentgenograms of heart and lungs, gall-bladder, and large intestine were negative, but studies of the stomach and duodenum suggested diverticulitis of the duodenum.

Because of an unexplained fever varying between 99 and 104° F., the patient was given sulfathiazole in adequate doses, after exhausting all laboratory tests conceivable to reach a final diagnosis. The medication was of no avail.

Ten sputa for tubercle bacilli, five stool cultures for typhoid bacilli, three agglutinations for brucella, typhoid and paratyphoid were all negative. The spinal fluid and blood were negative for syphilis. The cephalin cholesterol flocculation test was ++. The blood chemistry and the Addis sediment count were non-contributory.

He was discharged 44 days after admission, to be readmitted eight days later to the surgical ward with the same complaints as previously, but showing pain and swelling of ankles and intense precordial pain.

The blood pressure at this time had gone up to 174 mm. Hg systolic and 90 mm. diastolic (in a period of 52 days). His temperature was 100.4° F. His calf muscles were exquisitely tender, and his symptoms were very much intensified. The blood and urinary pictures were unchanged.

Three days after the second admission he started to have severe difficulty in breathing and expectorated bloody sputum. Twelve days later, while sitting on a chair in the ward, he died suddenly.

Necropsy: There were 75 c.c. of a cloudy, greenish-yellow fluid in the peritoneal cavity, and numerous old fibrous adhesions were seen in the region of the cecum. The liver weighed 1790 gm., was yellowish-brown in color, and congested. The right pleural cavity contained 1400 c.c. of a yellowish cloudy fluid mixed with large flecks of purulent material. The right lung was adherent to the parietal pleura by fibrino-purulent exudate. The left pleural cavity contained 600 c.c. of fluid identical to that on the right side, and fibrinous pleurisy was observed. The right lung weighed 1010 gm., and the left 815 gm. Bronchopneumonic consolidation was observed in both lungs, more marked on the right. The heart weighed 530 gm. The coronary vessels showed considerable beading. Two areas of recent infarction were seen in the left

ventricular wall. The right kidney weighed 220 gm., the left 230 gm. Over the entire surface of both organs many yellowish areas surrounded by hemorrhage were seen. When cut through, they were found to be pyramidal in shape and appeared to be softer than normal. The entire kidney substance appeared to be damaged severely by a combination of infarcts and abscesses. The testicles showed recent and old infarcts.

Microscopically, inflammatory lesions of the middle sized and smaller arteries were observed in the heart, kidneys, adrenal glands, testicles, spleen and pancreas. The earliest lesions consisted of hyalin necrosis of the media and perivascular infiltration with neutrophiles, eosinophiles and lymphocytes. More advanced damage was characterized by fibroblastic proliferation of the media, and thrombosis, both early and late. Some of the thrombi had organized and canalized. In the late stages, a scanty perivascular infiltration with lymphocytes was observed. Recent and old infarcts were seen in the kidneys, heart and testicles. No vascular damage was seen in the liver, but there were multiple areas of focal necrosis accompanied by hemorrhage. In some of the sections there was scarring, both perilobular and interlobular, accompanied in places by considerable bile duct proliferation. Throughout the affected areas there was a diffuse leukocytic infiltration, mainly of neutrophiles, lymphocytes and monocytes laden with blood pigment. The lungs showed bronchopneumonia and fibrinous pleurisy with empyema.

Diagnosis: Periarteritis nodosa of coronary, renal, adrenal, testicular, splenic and pancreatic vessels.

#### COMMENT

From the data obtained from a clinicopathologic analysis of seven cases of periarteritis nodosa collected from the records of two public hospitals of the City of Louisville certain conclusions are justified.

The etiologic agent is not evident in any instance. One of the patients (case 5) had been vaccinated against typhoid fever nine weeks previous to admission, and two (cases 4 and 6) had a rash, but none had been transfused with blood or plasma, nor had received horse serum. Inasmuch as a rash, regardless of type, is at least suggestive of allergy, we failed to clarify this point because sensitivity tests were not performed. Only one patient (case 7) showed definite eosinophilia, varying between 6 and 16 per cent, and had complained of what was interpreted as migraine for many years, but that information is not conclusive of allergy.

Two patients had a doubtful serologic reaction, and one gave a history of syphilis, but the lesions encountered could not be attributed to a syphilitic process. Evidence of latent syphilis was found in the testis and aorta in case 3. It is true that the giant cell, and the coagulation necrosis in the wall of the ruptured basilar artery suggest syphilis in this case, but the absence of vacuolization of the media, lymphocytic infiltration, splitting of the elastic membrane, and aneurysm formation of that type are against this diagnosis. There is enough gross and histologic evidence to show that it was an acute, explosive process.

In two instances (cases 4 and 6) there was a history of sore throat, suggesting a bacterial origin, but repeated blood cultures were negative. Neither can it be ascertained that bacterial allergy existed. Identical con-

clusions can be reached about the patients giving a history of gonorrhea. Four patients received sulfathiazole in adequate doses during their illnesses, but probably the drug had nothing to do with the disease.

Periarteritis nodosa is seen more frequently among males than females as evidenced by the ratio of 5:2; four were white and three colored. The ages varied from nine months to 50 years, with an average of 23.8 years. This is in disagreement with the reports of Harris et al.,<sup>12</sup> and it is of some significance in spite of the small number of cases analyzed in this paper. Furthermore, the finding of the disease in a nine month old infant is unique.

TABLE I  
Periarteritis Nodosa: Clinical Findings in Seven Cases

	No. of Cases	Percentage
Sudden onset.....	6	85%
Sudden death.....	6	85%
Tachycardia.....	6	85%
Fever.....	6	85%
Leukocytosis.....	6	85%
Neurological changes.....	6	85%
Dyspnea.....	5	71%
Cyanosis.....	4	57%
Weakness.....	4	57%
Neuritic pains.....	4	57%
Hypertension.....	4	57%
Albuminuria.....	4	57%
Anemia.....	4	57%
Edema.....	4	57%
Nausea and vomiting.....	4	57%
Headache.....	3	43%
Loss of weight.....	3	43%
Convulsions.....	2	30%
Epigastric pain.....	2	30%
Back pain.....	2	30%
Cylindruria.....	2	30%
Hematuria.....	2	30%
Sore throat.....	2	30%
Rash.....	2	30%
Cough.....	2	30%
Eosinophilia.....	1	15%
Pain in joints.....	1	15%
Hematemesis.....	1	15%
Chills.....	1	15%
Pain in testicle.....	1	15%
Hemoptysis.....	1	15%

The onset of illness was rapid in six, and insidious in one. Death was sudden in six; one recovered after a cerebral surgical operation and had been well for over a year (case 1). This is the first instance in the history of the disease in which surgery has been of benefit in periarteritis nodosa of the brain.

The most outstanding clinical findings were tachycardia, fever, leukocytosis, neurologic changes, dyspnea, nausea and vomiting, neuritic pains, weakness, albuminuria, anemia and hypertension (table 1). This is in partial agreement with previous reports.<sup>12, 35</sup> Among five patients from whom enough information was obtained, the average duration of the dis-

ease was 50 days, and the duration of symptoms before seeking medical care was 12 days. In five instances a clinical picture of subacute sepsis was observed, characterized by a temperature curve ranging from normal to 104° F.

Two cases were diagnosed before death. One had an exploratory laparotomy (case 2) because of a mistaken diagnosis of intractable peptic ulcer. Sections from a biopsy of the stomach and of the appendix revealed the typical changes of periarteritis nodosa. In case 1 the lesions were found in the brain substance removed at operation.

TABLE II  
Periarteritis Nodosa: Organs Affected in Seven Cases

Heart.....	5
Kidneys.....	3
Pancreas.....	3
Ileum.....	2
Spleen.....	2
Stomach.....	1
Appendix.....	1
Colon.....	1
Liver.....	1
Testes.....	1
Brain.....	1
Uterus.....	1
Basilar artery.....	1
Mesenteric arteries.....	1
Right common iliac artery.....	1
Adrenal.....	1

After a thorough analysis the data did not yield any symptoms or signs typical or even suggestive of the disease. Nevertheless, as observed by others<sup>38, 35</sup> and illustrated by cases 2 and 7 of this series, close observation of the changes in the blood pressure, especially if elevated rapidly in the presence of renal damage, may be of diagnostic aid. Undoubtedly this is a sign of very poor prognosis and rapid termination even in the absence of renal failure.

Contrary to other reports<sup>35</sup> renal damage was much less frequent among these patients and the damage observed was in accord with the clinical findings. The heart was involved in five instances (71 per cent), with aneurysmal dilatation of the coronary arteries in two cases. One of the aneurysms ruptured into the pericardial cavity causing death by tamponade; in the other, massive thrombosis occurred. In two others death was due to severe myocardial infarction.

One of the lesions was limited to the basilar artery with aneurysm formation and rupture causing death by pressure on the base of the brain. The brain damage in case 1 consisted of arterial occlusion by thrombosis and infarction of the right frontal lobe. The ileum was affected in two instances and the colon in one. None of these patients complained of diarrhea, but presented abdominal symptoms.

The spleen was damaged in two cases, but there was no evident enlargement. This is in agreement with previous reports,<sup>12</sup> and the relative infre-

quency and nature of the involvement of this organ tend to eliminate the possibilities of a bacterial etiology. The pancreas was damaged in three cases. This finding is of significance because of the rarity of the lesions among the cases reported by the other observers. The pathologic picture was identical with any other organ the site of arterial occlusion and infarction. The testicles, mesenteric arteries, uterus, stomach and appendix were each involved in one instance. The right iliac was damaged in one case and confirms the belief that the disease may extend into larger arteries. In three of the cases the veins were damaged. This is contrary to the findings of some other workers who consider the veins as rarely affected and in agreement with the reports of McCall and Pennock.<sup>52</sup>

Although the majority of the patients presented an enlargement of the liver at postmortem examination, only one showed vascular damage with infarcts. Pulmonary symptoms and death from bronchopneumonia were frequent, but no definite vascular lesions or infarcted areas were encountered in the lungs.

Microscopically some of the lesions were acute and of the exudative type in the larger and middle-sized and smaller arteries and in the veins characterized by coagulation and liquefaction necrosis of the media and profuse leukocytic infiltration. At this stage the exudate was composed of neutrophiles, eosinophiles, monocytes, lymphocytes and an occasional plasma cell infiltrating the media, adventitia and perivascular tissues. In the latter stages there was moderate to marked fibroblastic proliferation in the media and intima and a perivascular infiltration with lymphocytes, monocytes and less markedly by neutrophiles. Numerous recently formed and older thrombi were observed, many of them organized and canalized. A few healed lesions were seen, the vessel wall was thickened, the lumen decreased in diameter, and the perivascular infiltration scanty. Various degrees of atrophy, as well as infarction of the parenchyma, were observed, occurring more commonly in the heart, kidney, pancreas and spleen.

Initial inflammatory lesions in the adventitia independent of damage to the media were not observed after prolonged search on multiple sections. This tends to confirm the belief that the damage in periarteritis nodosa starts in the media and extends to the intima and adventitia. It was relatively easy to differentiate the lesions from those of thrombo-angiitis obliterans, bacterial arteritis and dermatomyositis. The difficulties in the differential diagnosis may be obviated by the close study of the lesion at different stages.

#### SUMMARY

Certain pertinent features in the clinical and pathologic picture of seven cases of periarteritis nodosa are hereby presented.

In none of the patients was a definite etiologic agent proved. In one the presence of eosinophilia and attacks of migraine, and in two others the appearance of a rash during their illnesses, suggested allergy.

Two cases were diagnosed before death by the pathologist. The majority presented a clinical course of subacute sepsis with such protean manifestations that clinical diagnosis was extremely difficult.

Two cases developed hypertension very rapidly in the presence of renal damage, their course was short, but death was not renal.

The case of a nine month old infant is presented; this is perhaps the youngest on record.

It seems that periarteritis nodosa of the brain may be curable, as evidenced by the recovery of one of our patients after surgical operation.

An unnecessary abdominal laparotomy is recorded, illustrating the mistakes in diagnosis due to the protean clinical manifestations of the disease.

The frequency of aneurysm formation, and involvement of veins in this disease, is discussed.

The very rapid onset and very short duration of illness of these patients show the fulminating character of this disease.

Microscopic studies of the lesions tend to indicate that the media is affected first and then the damage extends to both intima and adventitia with involvement of the perivascular tissues.

If the different stages are studied there should be no difficulty in distinguishing periarteritis nodosa from other forms of arteritis.

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# AN ANALYSIS OF COMPLICATIONS ENCOUNTERED DURING THERAPEUTIC MALARIA \*

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SINCE the introduction by Wagner-Jauregg<sup>1</sup> in 1917 of inoculation malaria in the treatment of neurosyphilis, thousands of patients have received this form of fever therapy. At a recently organized Army Neurosyphilis Center,† 300 patients, 75 per cent of whom had asymptomatic neurosyphilis and were in excellent physical condition, completed courses of 10 to 25 malarial paroxysms during an 11 month period from July 1944 to June 1945. Although racial immunity, previous attacks of natural malaria and the recent return of some patients from hyperendemic areas necessitated a number of reinoculations with heterologous malarial strains, 211 patients finally completed therapy with *Plasmodium vivax*, and 89 with *Plasmodium malariae*. At a time when natural malaria, recurring in veterans from overseas theatres, greatly influences the national health picture, it is felt that recorded clinical and laboratory observations of the complications encountered during the therapeutic use of the disease are of value in understanding its diverse manifestations. It is, of course, recognized that many of these complications will rarely be seen in Army patients, since treatment of natural malaria is promptly instituted, and few patients have more than two paroxysms.

The usual clinical features of malaria, i.e., anemia, lowered blood pressure, herpes simplex, gastrointestinal distress, muscular pain, cough, and weight loss are not considered in detail because of their relative benignity and constancy of appearance during the active febrile disease. The other clinical features are listed as complications in table 1 by incidence and time of onset, the latter in an effort to estimate roughly whether more numerous severe complications followed prolonged malarial therapy (more than 10 paroxysms).

*Jaundice.* Disturbance in hepatic function during therapeutic malaria with the development of clinical jaundice has been reported by Fong,<sup>2</sup> Dattner,<sup>3</sup> Kroll,<sup>4</sup> Winckel,<sup>5</sup> Kirby and Bunker,<sup>6</sup> and others. In a recent study of liver involvement in natural malaria, Kern and Norris<sup>7</sup> were impressed with the frequency of involvement of the liver in all species of malarial infection and in all stages of the disease. Of 1153 cases of malaria seen by these authors, 100 consecutive proved malarial patients were care-

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TABLE I  
Incidence of Complications Related to Time of Onset\*

Complications	IP	Paroxysms		Con	Total by Species	Sum Total	% of Total Series	
		1-10	11-25					
Jaundice	V	—	7	11	—	18	22	7.3
	Q	1	3	—	—	4		
Edema	V	—	2	10	1	13	21	7.0
	Q	—	3	4	1	8		
Albuminuria and hematuria	V	1	20	7	—	28	48	16.0
	Q	1	15	4	—	20		
Acute nephritis	V	—	1	—	—	1	4	1.3
	Q	—	2	—	1	3		
Neuritis and neuralgia	V	—	3	3	1	7	10	3.3
	Q	—	1	1	1	3		
Respiratory distress	V	—	6	3	—	9	13	4.3
	Q	—	4	—	—	4		
Pneumonitis	V	1	—	1	1	3	3	1.0
	Q	—	—	—	—	0		
Perisplenitis (and splenic rupture)	V	—	2	2	1	5	6	2.0
	Q	—	—	1	—	1		
Herpes zoster ophthalmos	V	—	—	—	—	0	1	0.3
	Q	—	1	—	—	1		
Hemorrhagic episodes	V	—	3	3	—	6	9	3.0
	Q	—	3	—	—	3		
Miscellaneous†	V	—	8	3	3	14	18	6.0
	Q	—	4	—	—	4		

Total No. Treated Cases Completed—300  
Vivax—211  
Quartan—89

Key:

\* Complications do not correspond to number of patients, multiple complications occurring in several instances.

† Includes tabetic crises (6); mental complications (5); urticaria (2); hyperlipemia (1); auricular fibrillation (1); convulsive seizures (2); hypocalcemic tetany (1).  
IP—Incubation Period. Con—Convalescence. V—Vivax. Q—Quartan.

fully studied for liver enlargement and changes in liver function tests. It was found that 60 per cent of the cases examined had palpable liver enlargement which fluctuated with the activity of the disease, increasing during the continuation of an active febrile attack and decreasing promptly following successful antimalarial therapy. Impaired hepatic function evidenced by increased blood bilirubin and by bromsulfalein retention, like the enlargement of the liver, varied with the activity of the disease. Eight of their 59 patients with palpable livers had marked tenderness in the right upper quadrant, but none had jaundice. The assessment of clinical jaundice was complicated by the previous use of prophylactic atabrine for long periods of time.

Kopp and Solomon<sup>8</sup> studied nine patients for impaired liver function during malarial therapy for dementia paralytica. Indication of decreased hepatic function was found in reduction of total blood cholesterol and cholesterol esters, in lowered excretion of hippuric acid, and in strongly positive reactions to cephalin flocculation tests. Less marked were reduction of phospholipid, retention of bromsulfalein, and changes in blood bilirubin. All of these tests invariably showed a return to normal function within three to six weeks. One patient in their series developed jaundice during treatment, but it was felt that this was conditioned by previous liver damage due to prolonged arsenical therapy. They suggested that impairment of liver function in malaria may be due to the large reduction in serum albumin with depletion of liver proteins. Recently, Mirsky, Vonbrecht and Williams<sup>9</sup> reported a series of 10 cases of malaria, two of whom showed bromsulfalein retention, but all of whom had positive cephalin flocculation tests.

Twenty-two cases of jaundice were encountered in the present series of 300 patients. Although 63 per cent of all those treated completed vivax malarial therapy, 76 per cent of the ones developing jaundice were in that group, demonstrating perhaps a slightly increased incidence of the complication in vivax malaria. No cases of jaundice developing after the termination of malarial therapy were encountered, in spite of the fact that approximately 35 per cent of the patients received 10 daily injections of mapharsen during their convalescence.

Of the total number of patients under malarial treatment, 74 (24.7 per cent) developed palpable enlargement of the liver. Splenomegaly, much more constant, was found in 242 cases (80.7 per cent), most of whom (203 cases) were treated with vivax malaria. Of the 22 presenting jaundice, nine had no gastrointestinal complaints and repeatedly showed negative direct van den Bergh reactions, but increased blood bilirubin. Icterus in these cases was considered to be the result of excessive red cell hemolysis. The other 13 cases, with clinical and laboratory evidence of impaired liver function, are summarized briefly in table 2.

The histories elicited from patients listed in table 2 revealed moderate alcoholism in six cases and previous attacks of natural malaria in four. All but one of the 13 had received arsenical and bismuth chemotherapy for at

TABLE II  
Jaundice

Patient No.	Age—Race	Malarial Species	History	Onset (No. Par.)	Clinical Symptoms	Liver Enlargement	Spleen Enlargement	Duration (No. Days)	Icteric Index	Cephalin Flocculation	v.d.B.		Status of Donor
											Direct	Indirect	
2	36W	V	Negative	15	Ankle edema	NP	1	6	24.5	4+	+	2.4	Mosquito
13	34C	Q	Negative	1P	Anorexia, vomiting	NP	1	14	100.0	4+	+	12.8	Normal
53	40W	V	Nat. malaria, arsenic dermatitis	19	Abd. pain, vomiting, dehydrated	NP	1	8	23.5	4+	+	—	Normal
107	26W	V	Negative	11	Anorexia	1	3	10	40.0	4+	+	2.6	Mosquito
122	38W	V	Alcoholic (mod.)	9	None	1	NP	6	45.0	4+	—	—	Mosquito
142	21W	V	Negative	8	Vomiting, dehydrated	1	1	6	26.6	4+	+	1.8	Normal
155	30W	Q	Nat. malaria, alcoholic (mod.)	9	Abd. pain, vomiting, anorexia	1	1	14	33.0	4+	+	2.9	Jaundiced
157	31W	Q	Nat. malaria	2	Abd. pain, vomiting, anorexia	2	PDI	10	74.0	4+	+	9.7	Jaundiced
187	34W	Q	Nat. malaria, alcoholic (mod.)	9	Vomiting, anorexia	2	2	14	31.7	4+	+	2.7	Normal
227	36W	V	Alcoholic (mod.)	15	Ankle edema, anorexia, vomiting	1	NP	10	36.3	4+	+	2.4	Normal
242	36M	V	Alcoholic (mod.)	14	Ankle edema, anorexia, nausea	NP	NP	15	42.5	4+	+	2.9	Normal
259	41W	V	Alcoholic (mod.)	8	Anorexia, vomiting, dehydrated	3	1	15	78.4	4+	+	18.4	Normal
475	39W	V	Negative	4	Vomiting, hiccough	2	2	9	21.1	4+	+	1.8	Normal

Key: W—White; C—Colored; M—Mexican; V—Vivax; Q—Quartan; Par.—Paroxysms; v.d.B.—van den Bergh reaction; Indirect v.d.B.—recorded as mg. % serum bilirubin; liver and spleen enlargement recorded as: NP—not palpable; PDI—Palpable on deep inspiration only; 1, 2, 3—palpability by number of fingers below costal margin.

least a six month period some time prior to the institution of therapeutic malaria. None had had previous attacks of hepatitis, but two were inoculated with the blood of a third patient who subsequently developed jaundice himself, suggesting the accidental transmission of an infectious type of hepatitis. In these two cases, the incubation periods from the time of inoculation to the onset of jaundice were 36 and 47 days. Their malarial (quartan) incubation periods were likewise prolonged to 32 and 30 days respectively. Neither patient had had antisyphilitic chemotherapy during the six months preceding inoculation. These findings suggested infectious hepatitis on the basis of blood transmission, rather than the so-called "homo-

logous serum jaundice" which usually follows a much longer incubation period.<sup>10</sup>

Cephalin flocculation tests were positive during active malaria in every one of 102 patients (including the 22 with visible icterus) who had had this test performed. The imminent onset of jaundice was predicted two to three days in advance from the bile-stained appearance of cells and debris in the urine sediments of several of those developing this complication.

Of the 13 patients with marked hepatic dysfunction, two showed remarkable improvement on supportive therapy, consisting of glucose infusions and a high carbohydrate and protein diet, without requiring interruption of malaria. In these cases, clinical remissions occurred within 14 days, although cephalin flocculation tests remained positive until after convalescence. The other 11 cases responded promptly to the same conservative measures plus the termination of malarial therapy by atabrine or quinine. In all 13 instances, cephalin flocculation tests became negative or minimally positive during the fourth week of convalescence. These observations led to a more intensive study of liver function in malaria related to treatment factors. A certain number of subsequent cases, during the course of therapeutic malaria, received additional supportive dietary and fluid intake as a prophylactic measure. At the same time, others received either partial or no additional therapy. Results of liver function tests and clinical observations in this study cannot yet be interpreted, but will be reported in a later communication.

*Edema.* The occurrence of edema during malarial activity cannot always be explained, and has stimulated several clinical investigations. Kopp and Solomon,<sup>11</sup> studying this complication in paretics receiving therapeutic malaria, associated it with low serum albumin (3 grams or less). They also found that edema occurring during the course of treatment in patients free from renal damage or cardiac failure was probably aggravated by an increase in the intake of sodium chloride, a not infrequent medication at institutions using fever therapy. Nineteen patients in the current series exhibited ankle edema during malarial therapy. In table 3, these are analyzed in relation to the several possible causative factors.

Thirteen of the 21 cases of edema had received vivax malarial therapy, representing an equal distribution when compared with the percentage of patients inoculated with each malarial species. Two of them were associated with acute nephritis, and two others with transient albuminuria. A low total serum protein (less than 5.8 grams) with a decrease in serum albumin to less than the critical level of 3 grams was found in 11 cases. In one of these, ascites and minimal pleural effusion developed, but disappeared after normal serum protein levels were reached. Impaired liver function with jaundice occurred in two patients, only one of whom demonstrated the serum protein changes. Hemoglobin fell to 8.7 grams (60 per cent) or less in nine cases, but not below 6.5 grams (44 per cent) in any. As noted in table 3, edema appeared in four of the patients while they were receiving

daily intravenous infusions of glucose in saline solution for either clinical jaundice or routine liver function studies. Sodium chloride perorally was withheld from all patients in this series. Signs of cardiac insufficiency were absent in all instances. The duration of edema varied from two to 30 days.

TABLE III

## Edema

Patient No.	Age—Race	Malarial Species	Onset (No. Par.)	Duration (No. Days)	Associated Disease	Hgb. (%)	Total Serum Protein	Serum Albumin	Serum Globulin	Urine		I.V. Infusions	Diet
										Albumin	Micro.		
2	36W	V	15	7	Hepatitis	68	5.8	2.7	3.1	—	—	N	Poor
40	38W	V	15	10	—	64	5.6	2.8	2.8	—	—	N	Fair
104	34W	V	22	5	—	54	5.6	2.9	2.7	—	—	Y	Poor
144	26W	Q	14	30	—	66	6.2	3.2	3.0	4+	—	N	Good
146	39W	V & Q	20	5	—	50	5.8	2.4	3.4	—	—	N	Good
149	42W	Q	15	10	—	50	5.4	3.5	1.9	—	—	N	Fair
150	37W	Q	con.	9	Nephritis	44	6.0	2.9	3.1	4+	Many RBCs	N	Fair
199	43W	V	15	4	—	48	6.6	3.2	3.4	—	—	N	Fair
227	36W	V	15	13	Hepatitis	70	6.1	3.5	2.6	—	—	Y	Fair
231	37W	V	8	6	—	78	6.0	3.8	2.2	—	—	N	Fair
235	31W	Q	4	17	—	74	6.9	4.0	2.9	2+	—	N	Good
245	30W	Q	7	11	—	80	6.6	3.8	2.8	—	—	N	Good
247	29W	V	20	6	—	66	5.6	3.2	2.4	—	—	N	Good
248	40W	V	24	10	—	50	6.8	4.4	2.4	—	—	N	Fair
282	33W	V	18	5	—	60	6.5	3.7	2.8	—	—	Y	Fair
335	27C	Q	4	2	Nephritis	90	5.6	2.7	2.9	4+	RBCs	Y	Good
338	29W	V	11	8	Hist. hep.	74	4.9	2.5	2.4	—	—	N	Poor
368	18W	V	15	4	—	64	5.4	2.7	2.7	—	—	N	Fair
403	37C	Q	12	3	—	58	6.3	2.7	3.6	—	—	N	Good
424	29W	V	9	2	Habitual alcoholism	98	5.4	2.7	2.7	—	—	N	Good
488	38W	V	13	15	—	46	4.8	2.8	2.0	—	—	N	Fair

Key: W—White; C—Colored; V—Vivax; Q—Quartan; Par.—Paroxysms; Hgb.—Hemoglobin; serum protein reported as grams per cent; I.V. Infusions: N—None; Y—Administered prior to the onset of edema; Con.—Convalescence.

Three of the patients (No. 231, 245, 247) on repeated examination, did not exhibit any decrease in serum albumin to within critical levels, or any change in albumin/globulin ratio or urinalyses. In these cases, anemia was not marked, and intravenous fluids and sodium chloride were not given. Although most of the cases of unexplained edema are probably due to individual variations in response to hypoalbuminemia, some may be initiated by transient anoxemia with increased capillary permeability during each malarial paroxysm when large numbers of erythrocytes are being destroyed.



*Albuminuria and Hematuria.* Albuminuria, lasting for two days or longer, was discovered in 48 of the 300 patients receiving treatment. Of these, 28 had vivax malaria and 20 quartan, indicating a relatively increased incidence of this apparently benign complication with the latter malarial species.

In Fishberg's<sup>12</sup> brief reference to malaria in the etiology of nephritis, he mentions the frequent appearance of albumin, red cells and casts in the urine of patients suffering from either natural or therapeutic malaria. With no other clinical findings exhibited, and with only exceptional cases sufficiently widespread to produce uremia, it was his belief that most of the cases fell into the classification of focal nephritis, although the older literature did not clearly differentiate focal from diffuse glomerulonephritis.

Nineteen of the 48 cases of albuminuria also showed varying degrees of microscopic hematuria. Eight (42 per cent) of these cases of combined albuminuria and hematuria occurred during quartan malarial therapy. Only one patient (vivax) developed a transient rise in blood non-protein nitrogen which promptly returned to within normal limits upon the termination of treatment. Two patients (quartan) developed ankle edema for which no other cause could be found. Of these, neither showed hematuria. Albuminuria and numerous pus cells were found in repeated urinalyses early in the febrile course of one patient who developed moderate urinary retention as the result of *tabes dorsalis*.

Although 75 per cent of this group of patients exhibited the complications prior to the tenth paroxysm, a large number of them were treated with quartan malaria and experienced a smaller average number of paroxysms than the comparable vivax group, thus diminishing the clinical significance of this figure. The duration of abnormal urinary findings varied from two to 31 days. They returned to normal spontaneously in 10 of the 48 patients while active malarial paroxysms were still taking place. The remainder of the cases, with one exception, showed prompt subsidence of the process during the first week of convalescence following the institution of antimalarial therapy. This single case continued to show albuminuria and hematuria for three weeks following termination of malaria, with improvement occurring only after considerable bed rest and dietary care. None of the patients developed intercurrent infections during their hospitalizations, and only two of the 48 had histories suggestive of previous kidney disease. Clinical evidence of acute nephritis did not appear in any of these cases. A further study of this group of apparently uncomplicated urinary changes, particularly in the repeated malarial attacks of the natural disease, may yield valuable information about the changes produced by a chronic recurrent focal nephritis, a condition, according to Fishberg, about which very little is known.

*Acute Nephritis.* Malaria as an etiological factor in acute nephritis has been mentioned repeatedly in the literature. Giglioli<sup>13</sup> described cases occurring particularly in patients afflicted with malaria of long duration,

associated with edema, impaired kidney concentration and hypertension. Thayer,<sup>14</sup> Heilig and Visweswar,<sup>15</sup> Dutt,<sup>15</sup> Fong,<sup>2</sup> and Kroll<sup>4</sup> each report instances of acute nephritis developing during active malarial attacks. Munk,<sup>16</sup> on the other hand, did not observe a single instance of renal disease in several thousand cases of malaria studied in Europe during World War I. Anatomical studies by various investigators in cases of nephritis occurring during malarial fever revealed for the most part the pathological picture of focal nephritis which was often very widespread, although occasional cases of diffuse glomerulonephritis existed.

Acute nephritis complicated the courses of four patients in this series. Three of the four received therapeutic quartan malaria. One had a vague history of low back pain for several years previous to therapy, and another had had natural malaria as a child. None had histories of hypertension or acute infections prior to fever therapy. No clinical evidence of streptococcal infection was present in any case. Smear and culture from a throat swab in one case did not reveal streptococci.

In three instances, the onset of nephritis was prior to the fifth paroxysm; in the fourth case, it was during the first week of convalescence while anti-malarial therapy (quinine) was still being administered. Urinary findings in each case consisted of 4-plus albuminuria and numerous red blood cells with varying numbers of granular and hyalin casts. Two patients developed ankle edema associated with a decrease in serum protein and reversal of the albumin/globulin ratio. Two of them developed a moderate rise in arterial blood pressure, one while malarial therapy was continued, and the other following its termination. Only one case, the most severe, showed a significant rise in blood non-protein nitrogen to 99 mg. per cent. Impaired renal concentration was found only in this single instance. Intravenous pyelography was performed in three of the four cases, but revealed no abnormalities. Cystoscopy was performed in one of these because of the marked, almost gross, hematuria, but no local urethral or bladder lesion was demonstrated. An attempt was made to stain smears of the urine sediment in each case, but malarial parasites could not be demonstrated within the erythrocytes.

The four patients with nephritis recovered completely from the acute attack following bed rest, controlled fluids, high protein diet and termination of malarial therapy. At least two of them could be classified as cases of diffuse glomerulonephritis, but one of these may have had an acute exacerbation of a chronic nephritic process. The other two cases probably represented severe attacks of focal embolic glomerulonephritis. All four yielded some evidence in favor of the view that malaria acted as a direct etiological factor in the production of kidney disease.

*Neuritis and Neuralgia.* There has been considerable difference of opinion among clinicians concerning the existence of peripheral neuritis of malarial origin. This complication is mentioned in the literature dealing with natural, but not induced malaria. Well-marked neuritis has been ob-

served in cachectic malarial patients where there was obvious predisposition to various infections and vitamin deficiencies.<sup>17</sup> DeLangen and Lichtenstein<sup>18</sup> reported several cases of neuritis in malaria with greatest involvement of the nerves of the lower extremities, although brachial plexus lesions were also encountered.

Neuritis associated with malaria has been observed in tropical regions in two forms. One,<sup>19</sup> with predominantly motor symptoms, usually unilateral, affecting the common peroneal and axillary nerves most frequently, was interpreted as a peripheral lesion, not specifically related to malaria. Subsequent malarial attacks after the appearance of the neuritic symptoms did not accentuate them. The other,<sup>20</sup> with predominantly sensory symptoms, usually bilateral and symmetrical, involving forearms and hands most often, was aggravated during subsequent attacks of malaria, and was more directly related to the disease. *Plasmodium vivax* was usually identified in this group, although the existence of falciparum infections could not be excluded because of their endemicity in the regions surveyed. It was found in this same series that the trigeminal, sciatic and axillary nerves were frequently the site of severe neuralgia during malarial attacks. Recovery was the rule following suppressive antimalarial therapy with atabrine. Other cases of severe trigeminal neuralgia<sup>21</sup> and of meralgia paresthetica<sup>22</sup> during attacks of malaria have been reported. Table 4 presents the findings in 10 cases of neuritis and neuralgia encountered during therapeutic malaria in this series.

Vivax malaria accounted for seven of the 10 instances of nerve involvement. The peripheral nerve syndromes observed were as follows: trigeminal neuralgia, ophthalmic branch—two; greater occipital neuralgia—two; brachial plexus neuritis (chiefly axillary nerve)—three; ulnar neuritis—2; common peroneal neuritis—two. The symptoms in each case were chiefly sensory, consisting of moderate to severe pain, paresthesia, hypesthesia or hyperesthesia. In addition, two of the 10 patients developed mild motor weakness. The neuralgias were characterized by severe radiating pain and residual tenderness in the absence of other objective neurological findings.

The duration of these neuritides varied from five to 35 days. Eight of the cases occurred during active malarial therapy, and the remaining two during the first week of convalescence. Two developed anemia with less than 10 grams (70 per cent) of hemoglobin. Pressure was considered a causative factor in ulnar neuritis when one patient frequently slept on the side involved. No other etiological explanations could be demonstrated.

In all instances, treatment consisted of analgesics and intravenous thiamine chloride over a period of at least 10 days. Three patients showed an excellent response to this treatment in less than one week. The remainder showed eventual improvement which could not be related to the administration of this drug. Relief of symptoms for 24 hours was obtained in one

TABLE IV  
Neuritis and Neuralgia

Patient No.	Age—Race	Malarial Species	Nerves Involved	Clinical Findings	Onset (No. Par.)	Duration (No. Days)	Hgb. (%)	Treatment and Response	Other Etiological Factors
1	37W	V	1. Trigeminal, ophthalmic div. 2. Greater occipital—left	Radiating, paroxysmal pain	1	8	100	Pantopon, codeine—Fair	None
16	36W	V	Brachial plexus, chiefly axillary nerve—left	Patchy areas of paresthesia, hyp- and hyperesthesia; deltoid muscle weakness	Con.	14	50	Physiotherapy, thiamine chloride—Good	On atabrine therapy
62	35W	V	Greater occipital—right	Radiating pain and point tenderness	6	21	100	Local procaine at nerve exit—24 hr. relief	None
95	34W	V	Brachial plexus, chiefly axillary nerve—left	Pain, numbness of left shoulder	4	14	100	Thiamine chloride—no relief	Marked psychogenic component
97	33W	V	Sciatic—bilaterally	Radiating pain down both thighs and legs	11	13	85	No relief until malaria terminated	No evidence of tabes dorsalis
107	26W	V	Ulnar—right	Hypesthesia, paresthesia in ulnar 2 digits	12	10	80	Thiamine chloride—excellent	? of pressure neuritis
150	37W	Q	Brachial plexus, chiefly axillary nerve—left	Pain, hypesthesia over upper arm; deltoid weakness	Con.	8	42	Physiotherapy and thiamine chloride—Good	On quinine therapy
155	30W	Q	Common peroneal right	Pain, paresthesia—antero-lateral aspect of right leg	25	10	74	Thiamine chloride—Fair	None
243	21C	Q	Trigeminal, ophthalmic div.—left	Radiating pain, tenderness over supra-orbital foramen	3	5	90	Spontaneous improvement	None
246	34W	V	Ulnar—right	Pain, hyperesthesia in ulnar 2 digits	14	35	68	Thiamine chloride—no effect	Pneumonitis

Key: W—White; C—Colored; V—Vivax; Q—Quartan; Con.—Convalescence (first week); Par.—Paroxysms; Hgb.—Hemoglobin.

case of greater occipital neuralgia by the local injection of procaine at the point of exit of the greater occipital nerve from the trapezius muscle, but recurrence of pain followed each subsequent malarial paroxysm. Physiotherapy was of definite value in restoring function to the two patients with motor lesions.

*Respiratory Distress.* Thirteen patients developed respiratory difficulty unaccompanied by pneumonitis. The following syndromes were observed: precordial pain and dyspnea—four; asthmatic wheezing—four; severe dyspnea and marked cyanosis—two; moderate dyspnea only—two; functional dyspnea—one. Except for the asthmatics, none was left with residual symptoms or signs following the completion of malarial therapy.

The clinical findings in the four cases developing severe precordial pain were minimal, consisting chiefly of tachycardia (100 to 140 per minute) during afebrile periods in two instances. No other cardiac changes were seen. Erythrocyte sedimentation rates were unreliable because of the elevations ordinarily encountered during active malaria. Repeated electrocardiograms during the attacks of pain and dyspnea were essentially unchanged in two cases, with only minimal changes in the other two—one showing a prolongation of the P-R interval from .18 to .20 second, and the other a decreased voltage of  $T_2$  and an isoelectric  $T_3$ . In the latter case, electrocardiograms prior to and following malarial therapy did not reveal this variation.

Four of the patients, two of whom had had similar previous attacks, developed severe bronchial asthma. Respiratory difficulty was most pronounced during the few hours at the height of the febrile paroxysm. Auscultation of the chest revealed loud rhonchi in each case. Symptoms began during the fourth paroxysm in the two patients with previous asthmatic histories, and during the third and fourteenth paroxysms respectively in those whose attacks were apparently primary. Roentgenographic examination of the chest during these episodes revealed no significant changes. Ephedrine and phenobarbital produced adequate relief.

Of the two patients who developed dyspnea only, one was markedly obese (270 pounds), and at best a poor risk for malarial therapy. A third patient developed dyspnea associated with marked nausea and vomiting, but was completely and immediately relieved during each attack by injections of sterile water.

Two patients presented extremely unusual and severe findings which have not been described elsewhere in the literature. Both experienced sudden onsets of severe dyspnea, orthopnea and deep cyanosis at the height of their paroxysms several hours following the termination of chills. One required oxygen and adrenalin during the acute episode. This patient ran an average parasitemia ranging between 15,000 and 25,000 parasites per cu. mm., but the other reached 75,000 per cu. mm. Both had quotidian vivax cycles and experienced no further difficulty following temporary interruption with thio-bismol. The severity of these attacks of dyspnea and cyanosis caused no little concern. During one such attack, breath sounds were not

audible in one patient's left lung, but returned 10 minutes later. There was no opportunity to perform bronchoscopy during any of the acute seizures.

*Pneumonitis.* The controversial aspects of infections of the respiratory tract associated with malaria have been adequately considered in a review of the literature with case reports by Applebaum and Shrager.<sup>23</sup> Their studies were of patients presenting pneumonitis in association with natural malaria in the Panama Canal Zone. They found the incidence of this complication compared with that of uncomplicated malaria to be 3.7 per cent,

TABLE V  
Pneumonitis

Patient No.	222	246	160
Age—Race	32W	34W	38W
Malarial species	V	V	V
Time of onset	Pre-patent period	13th paroxysm	Convalescence
Cough	Severe	Moderate	Severe
Chest pain	Left side	None	None
Hemoptysis	None	Moderate	None
Physical signs	Diminished breath sounds at left base	Transient râles at both bases	Numerous rhonchi and râles through both lung fields
X-ray findings	Small patch of parenchymal infiltration at left base obscuring costo-phrenic sulcus	Patchy increase in density in lower lobe, right lung; linear shadows in left lung	Patchy, rather dense infiltrations in both lungs
Hemoglobin (%)	80	52	100
WBC	7200 (40% lymph)	6000 (32% lymph)	10,700 (20% lymph)
Sputum	No organisms	No organisms	No organisms
Relation to malaria	Improved prior to onset of clinical malaria	Cleared promptly following atabrine therapy	Cleared with bed rest and pot. iodide

significantly higher than the occurrence of "primary pneumonitis" in non-malarial patients. From the variety of symptoms and signs, and from the laboratory findings and reactions to various treatment régimes, they offered the following classification of pneumonitis in malaria based chiefly on the therapeutic response: (1) atypical virus pneumonitis with inadequate response to therapy, but running a self-limited course; (2) bacterial pneumonitis with satisfactory response to sulfonamide compounds; (3) malarial pneumonitis with response to antimalarial therapy alone.

Three of the 300 cases reviewed in this series developed clinical and roentgenographic evidence of pneumonitis—one during the active febrile

illness, one during the incubation period and one during convalescence while on quinine therapy. Table 5 summarizes the findings in each case.

Only one of the three cases probably had a malarial pneumonitis. This patient's response to merely routine atabrine antimalarial therapy was rapid and complete. The one whose illness ran its course during the incubation period prior to the onset of clinically active malaria, probably had atypical pneumonitis of possible virus origin. The third patient, a deteriorated paretic, developed this complication on the fourth day of quinine therapy following a spontaneous remission from vivax malaria. The fact that he had a history of asthma and had worked in a nitrate munitions plant where he was occasionally negligent in wearing the prescribed air filter masks may have played a part in the production of his pneumonic process. The patchy infiltrations observed in roentgenograms of his chest disappeared with bed rest and potassium iodide medication, but recurred following a single injection of tryparsamide. Sputum examinations, repeatedly negative for tubercle bacilli and fungi, revealed no specific etiology. Gradual improvement subsequently ensued.

*Perisplenitis.* Enlargement and tenderness of the spleen, as noted in the discussion of hepatitis, is an almost constant feature of malaria. However, five patients in this series experienced such severe left upper quadrant pain with palpable and tender spleens, that a more severe reaction may have occurred, with extreme distention of the splenic capsule, splenic infarction, perisplenitis or a combination of these pathological processes as the underlying basis. On palpation, the size of the spleen in these cases varied from two to four fingers'-breadth below the left costal margin. The consistency was of two types. One, soft and boggy to touch and with a border difficult to locate, was the more tender. The other, firm and rubbery in consistency, had a sharp edge which rolled easily over the palpating finger. Auscultation of the splenic area was attempted in three cases, but a transient friction rub was heard during deep inspiration in one case only.

None of the patients in this group had had previous malarial attacks, but one had hepatitis following yellow fever vaccine inoculation in 1942. The total number of therapeutic paroxysms completed by each of the five patients in this group varied from 14 to 19, symptoms first appearing respectively during the second, fifth, thirteenth, and eighteenth paroxysms, with one onset during the second day of convalescence. One case developed a marked, though gradual, decrease in hemoglobin to 42 per cent (6.5 grams). Another's blood pressure dropped to 80 mm. Hg systolic and 40 mm. diastolic but promptly returned to within normal limits the following day. Four of the five patients completed courses of vivax malaria and the fifth quartan. In each instance, severe lancinating left upper quadrant pain appeared suddenly, requiring the patient to lie almost rigidly in bed and limit respiratory motions. Narcotics were necessary for relief of pain. Because of the severity of symptoms, malaria had to be interrupted in two cases. Two others gradually improved without intervention, but the fifth case suf-

ferred a prolonged attack, more definitely suggesting subcapsular splenic hemorrhage or infarction. This case is briefly reported.

*Case 79.* This 30 year old white male was treated with vivax malaria for asymptomatic neurosyphilis, group III. He had no history of previous attacks of natural malaria, and completed a total of 14 therapeutic paroxysms terminated with atabrine because of the persistence of albuminuria. Two days following the institution of atabrine therapy, while afebrile, he experienced sudden sharp pain in the left upper quadrant and left flank, aggravated markedly by inspiratory chest movement. The splenic edge was palpated two fingers below the costal margin. There was tenderness and rigidity in the left upper quadrant, and a bulge in the left flank. During that same day acute symptoms subsided without the development of generalized abdominal rigidity or tenderness. He continued to complain of dull aching pain in the regions involved during the subsequent week. In spite of the fact that malarial therapy had been discontinued and parasitemia was negative, he ran a low grade fever (100 to 101° F.) for one week following the onset of this complication. Urinalyses had been showing a gradual disappearance of albumin. White cells and differential blood counts remained within normal limits. Hemoglobin remained at 8.7 grams (60 per cent) for almost two weeks following termination of malaria, compared with the usually more rapid rise once antimalarial therapy has been started. A flat plate of the abdomen and intravenous pyelography revealed no abnormality other than an enlarged spleen. Approximately two weeks after the onset of this complication, his symptoms disappeared, temperature remained normal and hemoglobin gradually increased. From then on, convalescence was uneventful.

Spontaneous rupture of the spleen, a relatively rare and almost invariably fatal complication, was found in one of the two fatalities in this series. This patient died 45 minutes after the onset of symptoms of shock following a severe malarial rigor. Only one of the 31 reported cases of rupture of the spleen during therapeutic malaria survived following surgical intervention. A review of this material including a pathological study of the case encountered in this series will appear in a separate report.

*Herpes Zoster Ophthalmos.* Herpetic keratitis of the simplex variety associated with malaria has been described by Kipp,<sup>24</sup> Ellet,<sup>25</sup> and others. This form of keratitis is chiefly of the dendritic type and results in superficial ulceration of the cornea with photophobia and lacrimation. A recent review by Chamberlain and Bronson<sup>26</sup> of herpes simplex keratitis revealed that six times as many cases were found during an 18 month period from a malarial division of troops as from a comparable group that had not been exposed to this disease. In many of the cases described by these authors, neutralization tests revealed antibodies against a known strain of herpes simplex virus, with strongly positive cutaneous reactions to the herpes simplex antigen. Although numerous cases of herpes simplex labialis, a frequent accompaniment of malaria, were encountered in our series of 300 cases, herpetic keratitis was not seen. However, one patient developed an herpetiform eruption over the left upper lid associated with severe radiating supraorbital pain on the same side, presenting the picture of herpes zoster involving the ophthalmic branch of the trigeminal nerve. No other instance of ophthalmic zoster related to malaria could be found in the literature.



*Case 245.* This 31 year old white male was inoculated with quartan malaria for the treatment of asymptomatic neurosyphilis, group III. At the onset of his third paroxysm, he developed severe pain above and behind the left eyeball, radiating to the left temple. An herpetiform eruption appeared later that same day over the left upper eyelid. The severity of pain required the administration of narcotics. Although malarial therapy was continued, the herpetic eruption disappeared in approximately five days, but pain in the left eyeball and left supraorbital region remained during the rest of his malarial course, disappearing finally during the first week of convalescence. Corneal stains of the left eye examined during the acute attack and during the subsequent two weeks revealed no ulcerations, but it was felt that the findings were consistent with the clinical entity of herpes zoster ophthalmos.

*Hemorrhagic Episodes.* Skin and mucous membrane hemorrhages have been reported in cases of natural malaria, particularly with the falciparum and quartan species. Very few of these complications have been reported following the induction of therapeutic malaria. Kroll,<sup>4</sup> in his review of quartan malaria in the treatment of neurosyphilis, encountered repeated episodes of epistaxis in three separate cases. Greco and Ziedman<sup>27</sup> reported a single case of purpura complicating therapeutic quartan malaria. Manson-Bahr<sup>28</sup> reports purpura as a rare complication of malaria, leaving the impression that it is associated with blackwater fever. Tappeneir<sup>29</sup> cited a case of symptomatic purpura, occurring during vivax therapeutic malaria, which disappeared spontaneously in spite of the continuation of fever therapy. He concluded that this phenomenon was a result of capillary toxicosis such as occasionally occurs in other infectious diseases as the result of toxic injury to vessel walls.

Nine cases in this series exhibited spontaneous hemorrhagic episodes during active malarial therapy. Five had repeated episodes of epistaxis, one had epistaxis associated with considerable rectal bleeding and one developed multiple petechial skin hemorrhages. Hematemesis occurred in two cases. One had a previous history of duodenal ulcer, and the other had had a gastroenterostomy with partial resection of the stomach because of syphilitic gastritis and ulceration. In both, the bleeding was not severe and promptly disappeared when malarial therapy was discontinued and diet more effectively handled.

Three of the hemorrhagic episodes occurred during quartan malaria and the others were associated with vivax malaria. A study of some of the factors which might have been a basis for this increased bleeding tendency was undertaken during the periods of hemorrhage. Hemoglobin, quantitative parasite count, platelet count, bleeding time, clotting time and prothrombin time were recorded in each instance. Parasite counts did not exceed the normal range of vivax and quartan parasitemias. Two patients developed anemia with hemoglobin lower than 8.7 grams (60 per cent). In only one case was the platelet count low enough (120,000) to be considered within the thrombocytopenic range. There were no undue prolongations of bleeding time, clotting time or prothrombin time in any of the cases studied.

The relation of these hemorrhagic episodes to antimalarial therapy was not clear-cut. Three patients were started on atabrine after this complication developed and were free of symptoms the following day. The remaining five became symptom-free before the administration of antimalarial drugs. None had recurrences. Because of the rare appearance of purpura in therapeutic malaria (only three authentic cases in the literature), the single case in this series is reported:

*Case 161.* This 27 year old white male received quartan malarial therapy for asymptomatic neurosyphilis, group III. During his fourth paroxysm, minute hemorrhages appeared over both legs and forearms. No mucous membrane lesions could be found, and there was no edema or bleeding from the mouth or throat. His past history was essentially negative except for a previous attack of natural vivax malaria in 1935. Hemoglobin during this episode was 13 grams (90 per cent) with a malarial parasite count of 3,000 per cubic mm. Platelet count was 310,000; bleeding time four minutes; clotting time six minutes; and prothrombin time 21 seconds. A tourniquet test produced 15 to 20 petechial hemorrhages per square inch. Malarial therapy was not interrupted and the petechial lesions disappeared completely in five days. It was difficult to evaluate associated arthralgic symptoms because of the malarial malaise. No gastrointestinal bleeding occurred.

The relationship of hypovitaminosis C to a hemorrhagic tendency in malarial patients has been investigated. Reniger-Areshveva,<sup>30</sup> studying pregnant women, estimated the vitamin C content in the placentas of women suffering from malaria in comparison with healthy women on the same diet. They found an overall average in all seasons of 3.5 mg. per cent in malarial patients and 13.5 mg. per cent in healthy patients. The more severe the malaria, the greater was the reduction in vitamin C in all tissues. Although the vitamin C excretion in pregnant urine is normally low, they found 13.7 mg. per cent in malarial women and 27.5 to 41.9 mg. per cent in normal persons. The rôle of hypovitaminosis C must, therefore, be considered seriously when manifestations such as petechiae, stomatitis, gangrene of parts of the skin and abortion occur in malaria.

*Miscellaneous Complications.* The exacerbation of *tabetic crises and lightning pains* during malarial therapy was observed in six cases. Three of the six had previous histories of lightning pains with original onsets from one to four years prior to the current hospitalization. The remainder, although demonstrating the neurological signs of tabes dorsalis, had never experienced these symptoms previously. In all instances, lightning pains, radiating down both lower extremities, were most severe during the febrile paroxysms. Two patients had associated gastric crises with girdle-like sensations and almost continuous nausea and vomiting. Another one had rectal crises as well as lightning pains. Symptoms began, in the six cases, from the second to the seventh paroxysms.

Cochems and Kemp<sup>31</sup> treated 26 patients suffering from typical tabetic lightning pains with thiamine chloride given intravenously, but produced relief in only five patients. They concluded that thiamine chloride was valueless in the majority of cases for the alleviation of tabetic pains. The

use of thiamine chloride intrathecally by Stone<sup>32</sup> resulted in several instances of relief of lightning pains, visual disturbances, symptoms involving the bladder and improvement in gait. A recent report by Kesert and Grossman<sup>33</sup> revealed satisfactory results in the use of intraspinal thiamine chloride in eight cases of tabes dorsalis, several patients receiving more than one injection. Intrathecal administration of the drug was not considered to be necessary in any of the cases in our series, since complete relief invariably followed malarial termination. However, each patient developing crises received 100 mg. of thiamine chloride intravenously daily for a period of 10 to 14 days. Two showed a fairly good response in four or five days, but the remaining four were not relieved until malarial therapy was discontinued.

Transient hyperglycemia has been reported in patients suffering from tabetic crises, with relief of pain following the use of insulin.<sup>34</sup> In the six cases studied in this series, blood sugars, determined during the crises, varied from 74 to 94 mg. per cent. Three patients were placed on insulin (10 units b.i.d.) for as long as one week without symptomatic relief. Narcotics were the only effective agents in controlling these severe painful episodes.

*Mental complications* during and following therapeutic malaria were uncommon in this series. Vonderlehr<sup>35</sup> comprehensively reviewed the various mental syndromes appearing during therapeutic malaria, but the existence of dementia paralytica in the majority of instances confused the psychiatric picture. O'Leary<sup>36</sup> noted a large number of mental complications, from complete negativism to marked delirium, during the febrile stage of inoculation malaria. Singleton and Riley<sup>37</sup> pointed out that patients of manic temperament were apt to be delusional, excited and restless during the course of treatment. Bizarre cerebral manifestations are known to occur with falciparum malaria, rarely used therapeutically; and hallucinatory syndromes have been reported following the administration of atabrine. Although Gaskell and Fitzhugh<sup>38</sup> observed 35 cases of toxic psychosis among 7,604 atabrine-treated cases of malaria, evidence for a direct etiological relationship was far from convincing.

Five mental complications were encountered in this series. Three patients became confused, disorientated, irrational and delirious during the height of the febrile reaction. Another experienced hallucinations with extreme tension and irritability during atabrine therapy. These symptoms disappeared spontaneously by the sixth post-atabrine day. The fifth patient developed an acute psychotic episode with delusions, hallucinations and belligerency. This case has been reported separately.<sup>39</sup> The rôles of neurosyphilis, malaria, atabrine and a possible superimposed functional psychosis in the production of this disorder were considered in some detail.

*Urticaria* has been reported infrequently as a manifestation of malaria. Stitt<sup>47</sup> mentions that it may occur. Bhowmick<sup>40</sup> reported two cases of malarial urticaria, both of whom apparently showed hypersensitiveness to

malarial parasites in a hyperendemic area. He postulated that the sporulation of malarial parasites in the circulation liberated a definite but unknown product which causes allergy resulting in urticaria.

Two patients in this series developed urticaria and pruritus prior to the tenth malarial paroxysm. The fluctuation in the severity of symptoms was definitely related to the malarial cycle, tertian in one and quotidian in the other case. Urticaria was found to be most pronounced several hours following the chill with diminution in symptoms on fever-free days. Skin tests were performed, but no specific allergens were found, and no relation to medications could be demonstrated. In one instance, erythema and wheal-formation followed the intracutaneous injection of homologous blood.

Repeatedly chylous blood serum in fasting specimens was discovered in one case being studied with routine liver function tests. Cholesterol was reported to be 107 mg. per cent, and total blood lipids 600 mg. per cent (slightly above normal for the test employed). Prior to therapy and following convalescence, serum was non-chylous.

*Hyperlipemia* has apparently not been reported as a consequence of malaria, but Thannhauser<sup>41</sup> notes that it occurs in animal experiments where there is a depletion of serum proteins. The lowering of the colloid osmotic pressure by this decrease in protein was thought to play an important part in the release of the fat transport mechanism. Although this hypothesis has not been proved, many cases of hyperlipemia are reported associated with low serum protein. In spite of the fact that malaria often produces changes in blood protein levels with substantial decreases, repeated determinations of serum protein in this case revealed values above 6.1 grams per cent with normal albumin/globulin ratios.

A 60 year old patient, the oldest treated in this series, developed dizziness, restlessness, and a grossly irregular pulse rate following his third malarial paroxysm. Electrocardiographic studies confirmed the existence of *auricular fibrillation*, not recorded in previous graphs. Cardiac insufficiency was only minimal, and the rhythm returned to normal after digitalization. Digitalis was subsequently discontinued with no further complications. The risk of an intensive form of therapy in patients over the age of 50 must be appreciated.

*Hypocalcemic tetany* caused the second sudden fatality. Although hypocalcemia was suspected two days before death, and the patient received intravenous calcium gluconate during that time, he died during a severe laryngeal stridor and generalized tetanic convulsion. Pathological study revealed a greatly distended gall-bladder with a kinked cystic duct, but no other probable etiological factors. The possibility that this fatality was secondary to an anomalous biliary tract causing poor absorption of calcium from the intestines is considered in greater detail in a separately-appearing pathological report.

*Convulsive seizures* were observed in two other instances. Both patients were moderately deteriorated paretics. One had repeated generalized epi-

leptiform convulsions which, during a febrile paroxysm, entered the phase of status epilepticus, but were finally brought under control. The other experienced three Jacksonian seizures involving the right arm and right side of the face. These were followed by transient paralysis of the right arm for two to five hours, but no permanent neurologic residua.

### SUMMARY

1. The complications encountered in a series of 300 cases of neurosyphilis treated with therapeutic malaria, both vivax and quartan, are analyzed.

2. Jaundice, edema, mild renal damage and neural syndromes are relatively common features of untreated malarial infection. Though they presented clinical problems during active therapy, none was followed by permanent sequelae.

3. Hepatitis with jaundice can at times be adequately controlled by intravenous fluids and high carbohydrate and protein diet, without necessitating the interruption of malaria; but in most cases such interruption, at least temporarily, is indicated. Under active treatment, no case of jaundice persisted for more than 15 days. Excessive corpuscular hemolysis in the absence of impaired liver function accounts for almost 50 per cent of those cases developing icterus. The accidental transmission of an hepatotoxic agent with the blood inoculation of *Plasmodia*, observed in two instances in this series, may play an important rôle in the "malarial" hepatitis observed during the therapy of neurosyphilis. Recent studies of homologous serum jaundice differentiated from infectious hepatitis may clarify this observation in the future. The occurrence of the complication, however, in mosquito-inoculated cases attests, at least in some instances, to a more specific toxic effect of malaria on the liver. Predisposing hepatic damage by prolonged arsenical therapy or rare syphilitic involvement of this organ cannot readily be evaluated. The constantly positive cephalin flocculation test in malaria adds to the growing impression that this reaction is non-specific.

4. Although the causes of edema during active malaria may be multiple, hypoalbuminemia is probably the precipitating factor in most cases. Three cases of edema, with no adequate clinical or laboratory etiological explanation, are reported. The duration of edema did not exceed 30 days, and in most instances proper diet proved to be adequate therapy.

5. Episodes of albuminuria and hematuria during repeated malarial attacks may play a rôle in the production of a chronic recurrent focal nephritis. Abnormal urinary findings improved spontaneously during malarial activity in almost 25 per cent of the cases in which they appeared, and did not last longer than 31 days in any case once antimalarial therapy was instituted. Malaria is to be considered an etiological factor in acute nephritis, four cases of which were observed in this series.

6. The neurologic and psychiatric manifestations of vivax and quartan malaria are relatively benign and readily amenable to antimalarial therapy.

Two mental complications, one an agitated psychosis and the other an acute hallucinatory syndrome, may have been related to the administration of atabrine.

7. An unusual form of severe respiratory distress with cyanosis was observed in two instances. It was also found that bronchial asthma is markedly aggravated during malarial paroxysms.

8. Unusual cases of purpura, herpes zoster ophthalmos, urticaria, hyperlipemia, spontaneous splenic rupture, and hypocalcemic tetany complicating malarial infection are briefly described. Fatalities, the only two in this series of 300 malaria-treated cases, occurred in the latter two instances.

9. Although it is recognized that the course of repeated paroxysms in therapeutic malaria differs from that of natural malaria interrupted early in its cycle by antimalarial agents, its use presents an opportunity for the clinical study of the diverse manifestations of a disease, which, because of extensive military operations in hyperendemic areas, may occupy the national health stage for many years.

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# THE RESPONSE OF CIRRHOSIS OF THE LIVER TO AN INTENSIVE COMBINED THERAPY \*

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UNTIL this decade the diagnosis of cirrhosis of the liver was generally regarded as the death knell of the patient. Most clinicians looked on the unfortunate victim of this disease as a "hopeless" or incurable case; they were concerned only with the length of time remaining for the patient to live. When ascites developed, as a rule the only therapeutic measure of direct value was believed to be repeated removal of the ascitic fluid by paracentesis, with the final paracentesis to be performed by the pathologist on the autopsy table.

However, Patek's revolutionary studies in human patients<sup>1, 2, 3</sup> opened a new epoch in the treatment of cirrhosis of the liver. His work together with that of Hoagland at the Rockefeller Institute,<sup>4</sup> and of Fleming and Snell<sup>5</sup> at the Mayo Clinic initiated a renaissance of interest in the therapy of human cirrhosis. As a result of the recent advances made in the treatment of chronic hepatitis innumerable patients who heretofore were labelled as "hopeless" cases<sup>6</sup> are returning to good health.

This report deals with the results obtained from using various therapeutic combinations in the treatment of cirrhosis of the liver, or chronic hepatitis, in a series of 62 patients studied from 1938 to 1945. The value of the intensive use of a "combined" therapy in the treatment of chronic liver disease is demonstrated and an analysis of the various therapeutic combinations is presented.

The significant contributions to therapy which were combined and used to a maximum degree in the author's plan of treatment may be divided into three main categories, namely: (1) a maximum protein or "basic" diet, (2) vitamins and liver extracts and (3) certain specific agents such as methionine and choline.

1. Diet plays an important rôle in the improved therapeutic regime in hepatic cirrhosis. Numerous studies<sup>7-13</sup> have demonstrated the value of the high protein, high carbohydrate, minimal fat diet—which is now in use. This is in contrast to the high carbohydrate but low protein diet formerly prescribed in America for diseases of the liver.

2. Vitamins have been shown to be of significant therapeutic value, by the work of Patek,<sup>1</sup> Fleming and Snell<sup>5</sup> and Morrison and Swalm<sup>18</sup> in human patients; and by Rich and Hamilton,<sup>14</sup> György and Goldblatt<sup>15</sup> in

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animals, and by others.<sup>4, 10, 17, 21</sup> All of these investigators demonstrated the need for vitamin B complex in this disease. The use of crude liver extracts orally and parenterally originated in the French school of organo-therapy. In 1901, the French clinicians, Mouras and Cyr,<sup>20</sup> were among the first to use the oral administration of liver in the treatment of cirrhosis. Cyr reported excellent therapeutic results in 13 of his 26 cases treated solely by the oral ingestion of large quantities of liver. After a lapse of 40 years, Patek and Post<sup>2</sup> in 1941 reported similar results in a series of 57 patients using injectable liver extracts, Brewer's yeast and a diet containing a moderate amount of protein and an ample amount of carbohydrate. Crude liver extract therapy has been advocated also by numerous other investigators.<sup>4, 5, 6, 10, 18, 21</sup>

3. Certain specific agents were introduced in the treatment of experimental cirrhosis by György and Goldblatt,<sup>15</sup> Blumberg and McCollum<sup>22</sup> and others.<sup>23-26</sup> Choline, methionine, casein, betaine hydrochloride and cystine were used (reports have also appeared on the toxic effects of cystine<sup>27, 28</sup>). Success with these therapeutic innovations in experimental cirrhosis was followed by their use in human cirrhosis with such gratifying results as are reported by Broun and Meuther,<sup>29</sup> Russakoff and Blumberg,<sup>30</sup> György,<sup>28</sup> Gordon,<sup>31</sup> Barker,<sup>32</sup> the author and others.<sup>6</sup>

A history of alcoholism was present in 28 or 45 per cent of the 62 patients, and syphilis was known to be present in three cases or 5 per cent. Definite histories of dietary deficiencies were obtained from a considerable number of those patients in whom alcohol seemed to play a predominant etiologic rôle in the development of cirrhosis. Their diet appeared to have been particularly low in meat and dairy products. A difference in the pathogenesis of cirrhosis in man and in the experimental animal is suggested by the difference in their responses to the consumption of alcohol. Whereas alcohol is known to be the most frequent etiologic factor in the production of human cirrhosis of the liver, the vast majority of observers concede the fact that it is ineffective in producing cirrhosis of the liver in the experimental animal.<sup>36a-c</sup> However, the therapeutic concepts arising from the use of choline, methionine, betaine, vitamin B complex, yeast extracts, crude yeast, etc., which originated in experimental studies on cirrhosis in the animal, have been substantiated by studies of their use in human cirrhosis.

#### PLAN OF THERAPY

For purposes of comparing the value of therapy, the 62 patients were divided into three main therapeutic groups (tables 1, 2, 3). Each main therapeutic group was subdivided into subgroups, a and b, in order to separate those patients without demonstrable ascites from those with ascites, respectively.

I. The therapeutic group in tables 1a and 1b consisted of 23 patients, termed the "untreated" control group. These cases were treated from 1938

to 1940 by the methods then in current use. These older methods consisted of a high carbohydrate diet, intravenous glucose solution and, in the cases where ascites existed, mercurial diuretics together with paracentesis

TABLE Ia  
11 Cases of Chronic Hepatitis Untreated by Combined Liver Therapy, 1938-40  
No Ascites (Controls)

Case	Duration of symptoms before treatment (months)	Time before signs and symptoms improved (months)	Time before liver function improved* (months)	Time before return to normal activities (months)	Time before all physical signs disappeared (years)
1	8				
2	48				
3	4				
4	18				
5	6				
6	1	3	6	6	1
7	1			6	
8	5				
9	4	3	6		
10	15				
11	24	1	1		
Averages	1.5 years	3.5 months (3 cases)	4 months (3 cases)	6 months (2 patients)	1 year (1 patient)
				No return to normal—9 patients	No return to normal—10 patients

\* As measured by icterus index, bromsulfalein, urobilinogen and bile salt concentration tests.

TABLE Ib  
12 Cases of Chronic Hepatitis Untreated by Combined Liver Therapy, 1938-40  
Ascites (Controls)

Case	Duration of symptoms before seeking medical advice	Time after treatment before signs and symptoms improved* temporarily	Time before return to normal activity	Time before death†
1	2 years			12 months
2	8 years			2 months
3	1½ years			38 months
4	4 years	2 months	1 year	27 months
5	1 year	2 months	½ year	
6	½ year			
7	3 years			5 months
8	2 years			10 months
9	1½ years			8 months
10	1 year			20 months
11	½ year	2 months	1 year	
12	3 years			7 months
Average	2.0 years			14.3 months (9 cases)

\* Treatment with mercurial diuretics and ammonium chloride, paracentesis, palliatives, high carbohydrate diet, glucose intravenously.

† 3 cases survived at this time; case 6 is actively at work; cases 5, 11 are now invalids.

TABLE IIa

9 Cases of Chronic Hepatitis Treated by Liver Extract, Vitamins and Diet, 1940-1942  
No Ascites

Case	Duration of symptoms before treatment (years)	Time after treatment before signs and symptoms improved (weeks)	Time before liver function tests improved (weeks)	Time before return to normal activity (months)	Time before all physical signs disappeared (months)
1	1	1	4	4	6
2	14	3	4		
3	1	1	2	2	5§ *
4	2	3	4	5	12
5	30				
6	3	1	3	2	6†
7	2	2	2	5	9
8	1	2	3	3	
9	2				
Averages 1.7 years		3 weeks (7 cases)	4 weeks (7 cases)	4 months (6 cases)	8 months (5 cases)
				(No return in 3 cases)	(No disappearance in 4 cases)

§ Injection of crude liver extract from 2 c.c. to 5 c.c. given daily for 10 days, then every other day for one month; twice weekly thereafter as long as clinically indicated.

\* All liver function tests returned to normal after 18 months.

† All liver function tests returned to normal after 12 months.

TABLE IIb

10 Cases of Chronic Hepatitis Treated by Liver Extract, Vitamins, Diet, 1940-1942  
Ascites

Case	Duration of symptoms before treatment (months)	Time after treatment before signs and symptoms improved (weeks)	Time before liver function tests improved (months)	Time before return to normal activity (months)	Time before all physical signs disappeared (months)	Died months after therapy
1	10	4	1	3		
2	8	4	3		8	
3	5	2	1	8	8	
4	3	4	4	6	6	14
5	38					32
6	18					
7	28					1
8	41					29
9	14					
10	12	5	3			
Averages 1.3 years		4 weeks (5 cases)	2.5 months (5 cases)	6 months (3 cases)	7 months (3 patients)	19 months (4 cases)
				No return in 7 patients	No return to normal in 7 patients	

\* Injection of crude liver extract 2 c.c. to 5 c.c. given daily for 10 days, then every other day for a month; twice weekly thereafter for as long as clinically indicated.

TABLE IIIa

11 Cases of Chronic Hepatitis Treated by Combined Liver Therapy\* in 1943-1945  
No Ascites

Case	Duration of symptoms before treatment (months)	Time after treatment before signs and symptoms improved (weeks)	Time before liver function tests improved (weeks)	Time before return to normal activity (months)	Time before all signs and symptoms disappeared (months)
1	2	1	2	3	3
2	36				†
3	1	1	1	2	4†
4	48				†
5	12	3	4	4	4†
6	1	1	2	3	3†
7	12	4	4	3	12
8	4	2	2	2	6†
9	10	3	3	3	4
10	15	2	2	2	
11	18	2	2		
Averages	16 months	2.5 weeks (9 cases)	2.5 weeks (9 cases)	4 months (8 cases)	5 months (7 cases)
				No return in 3 patients	No return to normal in 4 patients

\* Liver extract, maximal protein diet, vitamins, methionine and choline.

† Bed-ridden with ascites subsequent to therapy.

‡ All liver function tests normal after 18 months.

TABLE IIIb

9 Cases of Chronic Hepatitis Treated by Combined Liver Extract Therapy,\* 1943-1945  
Ascites

Case	Duration of symptoms before treatment (months)	Time after treatment before signs and symptoms improved (weeks)	Time before liver function tests improved (weeks)	Time before return to normal activity (months)	Time before all physical signs disappeared (months)	Died months after therapy
1	12	2	2			†
2	6	2	2	2	3	
3	14	2	2	6	4	
4	3	1	1	5	5	
5	24					
6	24					†
7	60					2
8	18	4	21	4	6	
9	12					
Averages	2 years	2.5 weeks (5 cases)	2.5 weeks (5 cases)	4 months (4 cases)	4 months (4 patients)	2 months (1 case)
					No return to normal—5 patients	

\* Liver extract, maximal protein diet, vitamins, methionine and choline.

† Patients 1, 6, bedridden, poor prognosis.

and palliatives. In group 1b with ascites, both salt and fluid intake were restricted. Bed rest was required by most of the patients showing portal decompensation.

II. The group in tables 2a and 2b, consisted of 19 patients treated from 1940 to 1942 by Patek's regime<sup>1</sup> which was modified by the author. This regime consisted of a moderate protein-carbohydrate, low fat diet, supplemented orally by 25 grams of Brewer's yeast daily, and parenterally by the injection of 10 mg. each of thiamine chloride and niacinamide with 0.3 mg. riboflavin every other day and by 3 to 5 c.c. of whole liver extract injected every other day.

III. The group in tables 3a and 3b, consisted of 20 patients treated from 1943 to 1945, with an "intensive combined" plan of treatment, described in three parts below.

1. *Basic diet.* The basic diet consisted of a maximum protein, high carbohydrate, high vitamin, low fat diet of approximately 2500 to 4000 calories. This was given to the patients who were able to take a full, solid diet, in the general proportions of 200 to 300 grams of protein, 300 to 500 grams of carbohydrate, and 50 to 100 grams of fat. In the severely decompensated patient for whom a liquid diet was required, the caloric intake was necessarily low, but as soon as possible it was stepped up to the maximum. In most cases lean meat was eaten three times daily. At least one glass of skimmed milk was drunk with each meal and at least one was taken in between meals so that a minimum intake of six glasses was maintained daily. Cottage cheese and eggs were eaten daily. There was a very ample intake of vegetables and fruit juices.

2. *Liver extract and vitamins.* A whole unfractionated liver extract, prepared by physical and not by chemical means (by filtration), was administered intramuscularly in dosage of 3 to 5 c.c. daily for 10 days, then every other day for 10 days, and subsequently two to three times weekly as indicated by clinical progress. The extract was reinforced by vitamin B complex, so that each c.c. of liver extract contained a minimum of 10 mg. vitamin B, 0.3 mg. of riboflavin and 10 mg. nicotinamide. Injections of this extract caused comparatively little pain. In addition, one capsule of a high potency multiple vitamin preparation together with two capsules of a high potency vitamin B complex preparation were given three times daily. In those cases in which moderate or marked jaundice existed vitamin K, either in capsules or parenterally, was administered.

3. *Certain specific agents.* Two grams of methionine were administered in capsule form daily (as recommended by György).<sup>28</sup> Likewise two grams of choline in capsule form were given daily. Casein and cystine were supplied by the high intake of skimmed milk, and cottage cheese daily.

#### PATIENT MATERIAL

Karsner<sup>33</sup> and others have stated that most cirrheses of the liver were unitary in nature; he quoted Fiessenger<sup>34</sup> to the effect that "there is only one

cirrhosis of the liver." The following series of 62 cases of cirrhosis is therefore divided clinically into two main groups, viz. (a) patients without ascites, (b) patients with ascites or hepatic decompensation. In both groups, enlargement of the liver was present in variable degrees.

The ages of the patients varied from 16 to 64 years, with an average age of 52 years. The ratio of males to females was 4:1.

Symptoms of the compensated patients consisted usually of weakness, nausea and vomiting, abdominal pain or distress, loss of weight, anorexia, dyspepsia, hematemesis or constipation. Signs consisted of jaundice of the sclerae or skin, enlargement of liver or spleen, nosebleeds, hemorrhoids, low grade fever, mental disturbances, signs of nutritional deficiencies, dermatitis and polyneuritis. In the decompensated patients there were, in addition to the above, abdominal swelling, peripheral edema, dilatation of collateral veins and vascular "spiders." Improvement was measured clinically by the increase in strength, appetite and sense of well-being, by the disappearance of dyspepsia and hematemesis, and by objective improvement as manifested by reduction in ascites, jaundice, enlargement of the liver, dermatitis, etc. Functionally, favorable progress was reflected in the improvement in the function of the liver as measured by four tests employed routinely to determine the course of the disease.

The liver function tests were (1) the icterus index, (2) the bromsulfalein dye retention test (2 mg. per kilo dose), (3) the urobilinogen test and (4) the bile salt concentration tests of the author.<sup>35a-f</sup> The tests were conducted periodically at frequent intervals; all four were performed at the outset of the treatment, and one or more were repeated once every week during the first few months. Thereafter, all four tests were rechecked once every six months. Four tests were used because it is generally agreed that no one liver function test adequately surveys the total functional capacity of the liver. Serum albumin-globulin ratios and blood cholesterol-ester ratios were determined in some cases; they were not employed routinely because they did not reflect progress or retrogression as promptly as did the four routine tests described above.

Each patient in the series was studied and treated within the first year of the two year period allotted to his group. Thus a minimum of two years of observation was maintained for each of the three groups. This two year period was stipulated since a patient with cirrhosis is usually dead, deteriorating or recovering during the third year of the fully developed phase of the disease.

## RESULTS

A. The "control" group of 23 patients observed by the author from 1938 to 1940 is presented in tables 1a and 1b. As previously described, they were treated only by palliative measures and not by the present plan of therapy. These patients were "unselected."

Table 1a presents data of 11 compensated cirrhotic patients who had reported for treatment on an average of 1.5 years, i.e. from four months to four years after the onset of symptoms. These patients were all free of demonstrable ascites. It is seen that two of the 11 patients returned to "normal" activity after an average of six months, and that three patients revealed some improvement in liver function after an average of four months. Only one patient showed a spontaneous disappearance of all signs and symptoms to date. Table 1b presents a group of 12 control patients with ascites or portal decompensation. The average duration of symptoms before medical treatment was 2.0 years. Three patients showed temporary improvement in signs and symptoms in an average of two months and these three patients returned to some degree of normal activity in an average of nine months, although they still showed signs and symptoms of liver disease. Nine of the 12 cases died in an average of 14.3 months after presenting themselves for treatment.

A larger series of untreated "control" patients was available in the hospital records. However, it was felt that the statistical advantage gained by presenting a series of two or three hundred "record room" cases would have been greatly offset by the lack of personal appraisal of such case material.

B. A series of 19 cases of chronic hepatitis treated according to the modified Patek regime, as outlined under II, "Plan of Therapy" is described in tables 2a and 2b.

Table 2a shows nine cases without ascites whose symptoms had lasted for an average of 1.7 years. Signs and symptoms improved after an average time of three weeks in seven cases, the function of the liver improved in these seven cases after an average time of four weeks. Six cases returned to moderate activity in an average of four months; five cases had a remission in their signs and symptoms in an average of eight months. Table 2b shows 10 cases with ascites in whom the signs and symptoms improved after an average of four weeks; improvement in the function of the liver occurred on an average of 2.5 months. Three cases returned to normal activity in an average of six months; three patients had a remission in their signs and symptoms in an average of seven months. Four cases terminated fatally in an average time of 19 months.

C. Tables 3a and 3b present 20 cases of chronic hepatitis treated by the intensive plan of "combined" therapy already described.

Table 3a shows 11 compensated patients with an average history of 16 months with symptoms. Nine of these required an average of 2.5 weeks before improvement of signs and symptoms and liver function became manifest. Eight cases returned to full normal activity in an average time of four months, while seven cases had a remission in signs and symptoms in an average of five months.

Table 3b presents nine patients with ascites who received the intensive "combined" therapy. Of these 5 showed improvement in signs and symp-

TABLE IVa  
Comparison of Results of Therapy in 31 Patients with Chronic Hepatitis  
No Ascites

	11 "untreated" controls 1938-1940	9 patients treated by diet, liver extract and vitamins 1940-1942	11 patients treated with liver extract, diet, vitamins, methionine and choline 1943-1945
Duration of symptoms preceding treatment (years)	1.5 years	1.7 years	1.3 years
Improvement in signs and symptoms after treatment	3 cases (3.5 months)*	7 cases (3 weeks)*	9 cases (2.5 weeks)*
Improvement in liver function tests	3 cases (4 months)	7 cases (4 weeks)	9 cases (2.5 weeks)
Return to normal ac- tivities	2 cases (6 months)	6 cases (4 months)	8 cases (3 months)
Remission of all signs and symptoms	1 case (1 year)	5 cases (8 months)	7 cases (5 months)
Died	3 cases (1 year)	1 case (9 months)	0

\* Average of time for cases listed.

TABLE IVb  
Comparison of Results of Therapy in 31 Patients with Chronic Hepatitis  
Ascites

	12 "untreated" controls 1938-1940	10 patients treated by diet, liver extract and vitamins 1940-1942	9 patients treated by diet, liver extract, vitamins, methionine and choline 1943-1945
Duration of symptoms preceding treatment (years)	2 years	1.3 years	2 years
Improvement in signs and symptoms after treatment	3 cases (2 months)*	5 cases (4 weeks)*	5 cases (2.5 weeks)*
Improvement in liver function tests		5 cases (2.5 months)	5 cases (2.5 weeks)
Return to normal ac- tivities	2 cases (24 months)	3 cases (6 months)	4 cases (4 months)
Remission of all signs and symptoms		3 cases (7 months)	4 cases (4 months)
Died	9 cases (14.3 months)	4 cases (19 months)	1 case (2 months)

\* Average of time for cases listed.



toms as well as liver function in an average time of 2.5 weeks. Four cases returned to normal activity in an average period of four months, and four showed a remission of signs and symptoms in an average of four months. One case died in two months, whereas two remained bedridden with a poor prognosis. The remaining three patients were capable of normal activity although one feared to return to his previous occupation.

D. Tables 4a and 4b compare the results obtained in the treatment of cirrhosis with the "pre-Patek" therapeutic methods (1938-40), a modified Patek regime (1940-42) and the intensive "combined" therapy (1943-45).

Table 4a gives the results of the series with portal compensation. There were three deaths among the "untreated" controls (1938-40), one death following the modified Patek regime (1940-42), and no deaths after use of the intensive combined therapy. Again, in the controls, only two cases were able to return to normal activity in an average of six months, in the modified Patek group six cases returned in a four month average, and in the intensive combined group eight cases in an average of 3 months. Similarly, clinical and liver function improvement was present in only three cases of the control group, whereas it occurred in seven cases of the modified Patek group and in nine cases of the intensive combined therapy group. A remission of all signs and symptoms occurred in one case of the control group after one year, in five cases of the modified Patek group after an average of eight months, and in seven cases of the intensive combined therapy group after an average of five months.

Table 4b, giving the results of the series with ascites, shows that temporary clinical and liver function improvement occurred in three of 12 cases of the untreated controls in an average of two months (1938-40), whereas such improvement was present in five cases of the 10 in the modified Patek series in an average of four weeks, and in five cases out of nine in group 3a in an average of 2.5 weeks. Return to normal activity took place in two cases out of 12 controls in an average period of 24 months whereas it occurred in three cases out of 10 in the modified Patek group in an average of six months and in four out of nine cases in the intensive combined therapy group in an average of four months.

Death occurred in nine of the 12 control cases after an average period of 14.3 months. Four cases of the 10 of the modified Patek group died after an average period of 19 months. Finally, one case of the nine in the intensive combined therapy group died after two months of treatment.

#### COMMENT

Since the disagreement among various investigators as to the specific value of individual therapeutic agents such as choline, liver extract, or methionine, possibly was due to the interaction or synergistic action of the various principles contained in the therapeutic agents described in this paper, and since these principles were not completely understood, it appeared

justified to incorporate all those agents which had shown definite therapeutic value in both the experimental animal and in man. As is well known, when first tried penicillin therapy of subacute bacterial endocarditis was a failure because of inadequate dosage. Better results were secured later when intensive penicillin therapy was instituted. Similarly, better results were obtained in the series (1) when the liver extract injections were administered daily instead of twice weekly, (2) when the dosage of liver extract was stepped up to a maximum of 5 c.c. at each injection, (3) when the intake of vitamin B complex was similarly increased both by injection and by mouth and (4) when the intake of protein, both animal and vegetable, was stepped up to a maximum tolerance by three meat servings daily, accompanied by large quantities of skimmed milk, etc. If, as so many observers now believe, cirrhosis of the liver is a disease of nutritional deficiency, the indication is to "push" and "force feed" a nutritious "liver" diet to the point of maximum tolerance.

The therapeutic results reported preliminarily in this paper suggest that further trial of this maximal "combined" therapy is warranted in a greater number of cases and over a longer period of time. Striking improvement and even complete recovery was observed in cases which were formerly considered hopeless and progressing to fatal termination. When begun early in the course of the disease an intensive combined therapy frequently arrested the progress of the disease, enabled the patient to return to useful activity and often restored to him good health and a sense of well-being. Some observers have gone as far as to report that on an adequate therapeutic regime "almost unbelievable improvement has been observed in patients with severely decompensated cirrhosis."<sup>6</sup> In the author's experience this is undeniably true also in the majority of patients without decompensation.

#### SUMMARY

1. A small but carefully controlled series of 62 patients with chronic hepatitis was divided into three groups each treated for two years over an eight year period of time.

2. One group of 23 patients was treated only by such methods as were in use in 1938, that is by paracentesis, diuresis, high carbohydrate diet and palliative therapy; this group contained 11 cases without ascites and 12 cases with ascites, and was called the "untreated" control group.

3. A second group of 19 cases was treated by a modified "Patek" regime consisting of a nutritious high protein, moderate carbohydrate, low fat diet, liver extract injections and vitamin B complex therapy. This group contained nine cases without ascites and 10 cases with ascites.

4. A third group of 20 patients was treated intensively with a combined therapy which consisted of a maximum protein (three meat servings daily, plus skim milk), high carbohydrate, low fat diet, daily injections of 5 c.c. of a "whole" liver extract, highly potent injections of vitamin B complex,

daily oral vitamin B complex and multiple (total) vitamin capsules orally, together with 2 grams each of methionine and choline daily. This consisted of 11 cases without ascites and nine with ascites.

5. Treatment with the intensive combined method of therapy resulted in reducing the mortality rate in the compensated group (without ascites) over a two year period of time to 0 (1943-45) as compared with 27 per cent mortality in the control group (1938-40). The intensive combined therapy in the group with ascites reduced the mortality rate from 75 per cent in the control group (1938-40) to 11 per cent in the treated group (1943-45).

6. Treatment with the intensive combined therapy resulted in a sharp reduction in the length of the disability period of from 82 per cent (1938-40) to 28 per cent (1943-45) in the groups without ascites; from 83 per cent (1938-40) to 66 per cent (1943-45) in the groups with ascites.

7. The intensive combined method of therapy resulted in a remission of all signs and symptoms in 64 per cent of cases of the group without ascites, as compared with remissions in only 10 per cent of cases in the control group; in the group with ascites remission occurred in 34 per cent of cases as compared with none in the corresponding control group.

### CONCLUSIONS

1. The intensive combined method of therapy for cirrhosis of the liver used consists of administering a maximal protein, low fat, high carbohydrate diet in which protein is forced to maximum tolerance by three meat servings and at least six to eight glasses of skim milk and cottage cheese daily. This basic diet is supplemented by daily injections of 5 c.c. of a whole liver extract fortified with high potency vitamin B complex in large dosage, by oral vitamin B complex and multi vitamin capsules and by two grams each of methionine and choline daily.

2. Such a method resulted in a sharp reduction of mortality, morbidity and disability rate in the series of patients presented.

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# CASE REPORTS

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## ACUTE BACTERIAL ENDOCARDITIS; A CASE REPORT WITH RECOVERY AFTER TREATMENT WITH PENICILLIN\*

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THE term endocarditis may be defined as an inflammation of the lining membrane of the heart, often peculiarly limited to the valves of the heart, when the term valvulitis may appropriately be applied. In some instances the lesion is relatively slight with limitation to a single valvular cusp, to a small area of the mural endocardium, to a papillary muscle, or the lesion may be only a part of an extensive involvement of the heart, a pancarditis, in which the predominating symptoms and signs may be endocardial, myocardial or pericardial.<sup>1</sup> For clinical purposes, however, the term endocarditis should be divided into two groups.<sup>2</sup> The first form is the non-bacterial endocarditis which is usually rheumatic in origin. This form (also called "simple endocarditis") often leads to valvular deformities and the subsequent manifestation of chronic rheumatic valvular disease of the heart. In this form bacteria are rarely recovered from the blood stream or from the heart valves.<sup>2</sup> The second form may be called bacterial endocarditis. In this second form bacteria are usually recovered from the blood stream and heart valves, although in certain instances this is difficult of accomplishment. The bacterial form is conveniently subdivided into two groups, subacute and acute. Subacute bacterial endocarditis has been discussed at length in the literature and will not be discussed in this paper.

In a review of the literature one is impressed with the paucity of reports of acute bacterial endocarditis (also called "ulcerative endocarditis" and "malignant endocarditis") with recovery regardless of the form of therapy employed. The following case, in which recovery occurred, therefore, merits reporting.

### CASE REPORT

Mrs. M. L., a 33 year old separated white female electrician entered the Boston City Hospital on April 8, 1944 with the chief complaint of "inability to walk."

*Present Illness.* The patient had been in comparatively good health until two weeks prior to entry, at which time she became nauseated and was seized with sharp right lower quadrant pain, indefinitely located and vaguely described. The pain subsided in a few minutes, leaving no residual soreness, and was unaccompanied by other symptoms. She had had similar attacks of pain dating back to the age of 12, always occurring without relationship to food, nausea or vomiting, and always without other symptoms. About one week prior to entry she was seized with a similar attack "much more severe than ever before" compelling her to go to bed. On awakening the following morning she felt feverish but had no chills or chilly sensations. The pain, as previously described, was still present but not so severe. The

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patient stated that she was very drowsy and had slept most of the time for the following four days, but for a period of three days prior to entry she had been delirious and restless and was unable to sleep. During this period she complained of an intense throbbing headache located in the temporal and supraorbital regions with a constant tinnitus. She had also noted some vertigo when she attempted to walk, with a tendency to stagger to the left.

The family history was entirely negative. The past history revealed that she had been treated for years at the out-patient department for some pelvic disorder, the exact nature of which could not be determined, but which was characterized by periods of intermittent vaginal discharge not definitely related to the previously described episodes of vague abdominal pain. The system review was negative.

*Physical Examination.* Physical examination at the time of entry revealed a well developed, well nourished, and well oriented middle-aged female lying in bed in no apparent acute distress. The temperature was 105° F. rectally, pulse 120, and respirations 30 per minute. The head was negative; no tenderness could be elicited over the temporal and supraorbital regions. The eyes, ears, nose and throat were negative. The teeth were in good condition. The neck revealed no adenopathy; no stiffness was present. The chest was clear and resonant, and no râles were heard. The heart was not enlarged, the rhythm was regular, the rate 120, and no murmurs could be heard. The second aortic sound was greater than the second pulmonic sound. Blood pressure was 95 mm. Hg systolic and 55 mm. diastolic in the right arm, and 95 mm. Hg systolic and 60 mm. diastolic in the left arm. The abdomen was symmetrical; no masses or viscera could be felt. Slight tenderness was elicited in the right lower quadrant with some voluntary spasm over the entire lower abdomen. The skeleton was negative. Rectal examination was negative. Vaginal examination revealed a multiparous introitus and bilateral lacerations of the cervix which was non-tender and freely movable. The vaults were thought to be clear, and a slight bloody discharge was noted. The extremities, except for slight clubbing of the fingers, were negative. The reflexes were physiological; no pathological reflexes were elicited.

It was obvious that the patient was suffering from an acute fulminating infection, the source of which could not be determined at this time. A tentative diagnosis of septicemia with a questionable brain abscess was made.

*Laboratory Data.* Laboratory studies at this time revealed a negative urine. The hemoglobin (Sahli) was 84 per cent. The leukocyte count was 7800 with 90 per cent polymorphonuclear leukocytes, 5 per cent lymphocytes, and 5 per cent monocytes. The blood Hinton reaction was negative, and the blood non-protein nitrogen was 25. Lumbar puncture performed at the time of admission and two days later was negative. A blood culture taken at this time yielded (48 hours later) a pure growth of alpha prime hemolytic streptococcus.

*Progress.* On the day following admission the patient appeared to be much sicker than at the time of entry. Further examination revealed increased tenderness in the right lower quadrant. Vaginal examination at this time revealed a cervix which was tender on motion, and the presence of a tender, fluctuant, lemon-sized mass in the right vault. These findings were confirmed by gynecological consultation. A cervical culture revealed alpha prime hemolytic streptococcus in pure growth, the same organism which was recovered from the blood stream. It then became apparent that the patient was suffering from a septicemia arising from a focus of infection in the pelvis. Her condition was critical, and sulfonamides were given at once. The patient was seen in consultation by Dr. Maxwell Finland, who, in view of the usual susceptibility of alpha prime hemolytic streptococcus to sulfonamides, recommended their immediate use. Five grams of sulfamerazine were given intravenously daily together with parenteral fluid for a period of seven days. Several small supportive

transfusions were also given, and the patient's nutrition was maintained by the use of White's Mixture given by a Levine tube. Considerable improvement resulted from this régime, but her condition was still serious.

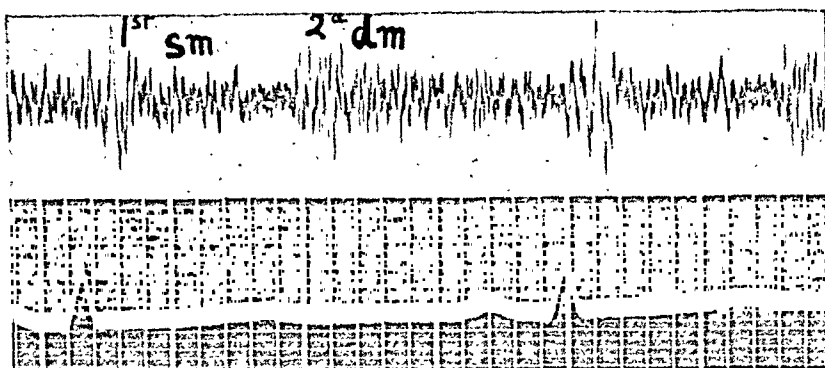


FIG. 1. Electrocardiogram in Lead I and apex phonocardiogram. Stethoscopic microphone; amplif. = 6; sm = systolic murmur; dm = diastolic murmur.

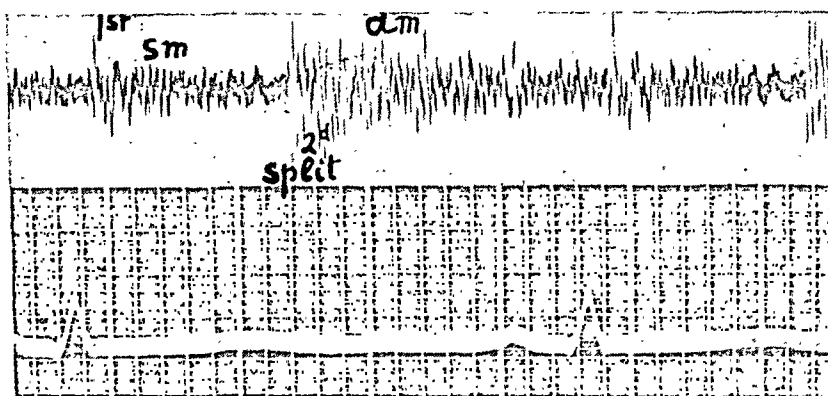


FIG. 2. Electrocardiogram in Lead I and phonocardiogram recorded over the pulmonic area. Stethoscopic microphone; amplif. = 6; sm and dm—same as above; split 2 = split second sound.

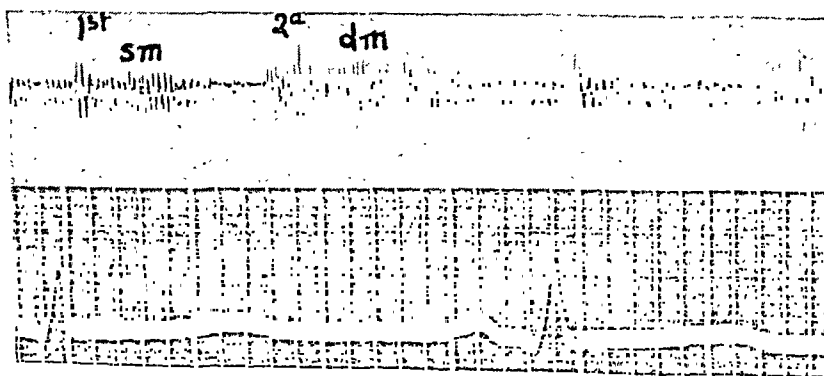


FIG. 3. Electrocardiogram in Lead I and phonocardiogram recorded over the aortic area. Logarithmic microphone; amplif. = 7; sm and dm—same as above.

On April 17, nine days after admission, iridocyclitis was noted in the right eye. Following consultation with the Ophthalmological Service this was treated by iridectomy, warm boric acid compresses, and atropine. This complication had little



or no influence on the subsequent course of the disease, and it was felt that the infection was metastatic in origin although no organism could be cultured from the affected eye. By this time the cervical culture had become negative, but the blood culture was still positive for alpha prime hemolytic streptococcus. It was felt that treatment with sulfamerazine had been unsuccessful in spite of an adequate drug level (free 24.0 mg., total 26.8 mg.) and the absence of complications from drug therapy. The susceptibility of the infective agent to penicillin was tested, and since it proved to be highly susceptible, this medication was used. One hundred thousand units of penicillin were given intravenously for the first day, and thereafter 15,000 units were given intramuscularly every three hours for a period of 11 days, a total dosage of 1,420,000 units.

On the evening of April 19 the patient suddenly became dyspneic, orthopneic and cyanotic. Coarse moist râles were heard at the bases, and for the first time a loud, high-pitched diastolic murmur, grade IV, was heard with maximal intensity over the aortic area. A systolic murmur was also heard at the apical and basal regions. The blood pressure at this time was 120 mm. Hg systolic and 50 mm. diastolic (previously 95 mm. systolic and 60 mm. diastolic), and a 1+ pitting edema of the lower extremities was noted. No petechiae were seen. She was given morphine and oxygen at once, and full digitalization was instituted. It was felt that the infection had now involved the aortic valve, causing acute aortic regurgitation and heart failure. The prognosis seemed hopeless at this time, but a good response to therapy was obtained.

By April 21 her temperature had reached a normal level, and except for otherwise explainable occasional slight rises it remained normal thereafter. Repeated electrocardiograms and seven foot chest plates revealed no evidence of cardiac disease in spite of the persisting diastolic murmur. By this time the patient was on a daily maintenance dose of digitalis which was discontinued four days later because of excessive nausea and vomiting. The blood culture had become negative and remained so thereafter. Examination revealed no changes in the cardiac status, and there was no evidence of decompensation. Although the pelvic mass was still present and pelvic findings were unchanged, it was deemed inadvisable to drain the suspected abscess at this time.

On May 7 a presystolic gallop rhythm was heard and digitalization was begun again. Except for the gallop rhythm there was still no evidence of cardiac strain. An electrocardiogram at this time was negative, and a seven foot heart plate showed no evidence of cardiac dilatation. Phonocardiograms taken by Dr. A. Luisada revealed tracings which were consistent with the clinical diagnosis. The tracings and their interpretation are shown below.

*Interpretation.* "There is a loud diastolic murmur composed of both high and low vibrations. This murmur has its maximal intensity over the third left interspace and occurs immediately after the second sound. It is well transmitted both to the apex and the aortic area. It decreases gradually during diastole, but continues until the next first heart sound begins. There is also an apical and basal systolic murmur of decreasing intensity in the second half of systole. The second sound is split over the base. Presystole cannot be accurately studied owing to the exceptionally long duration of the diastolic murmur.

"The apex cardiogram gives evidence of a high auricular wave (auricular gallop). Cardiograms recorded over the third left interspace show a very high and abrupt wave of rapid filling immediately after the second sound.

"The above findings are consistent with the existence of a large aortic regurgitation, of a mitral regurgitation (? functional), and stasis of the pulmonary circulation."

On July 14 the patient was allowed out of bed for gradually increasing periods and rapidly regained her strength. Except for the disappearance of the presystolic gallop rhythm the cardiac findings were unchanged. An electrocardiogram showed

for the first time evidence of myocardial involvement. During convalescence it was determined that the patient no longer needed digitalis, and she was discharged on July 28, seventeen weeks after admission.

When seen five months later her condition was unchanged, she felt well, was able to work, and presented no evidence of cardiac decompensation. The aortic diastolic murmur was still present.

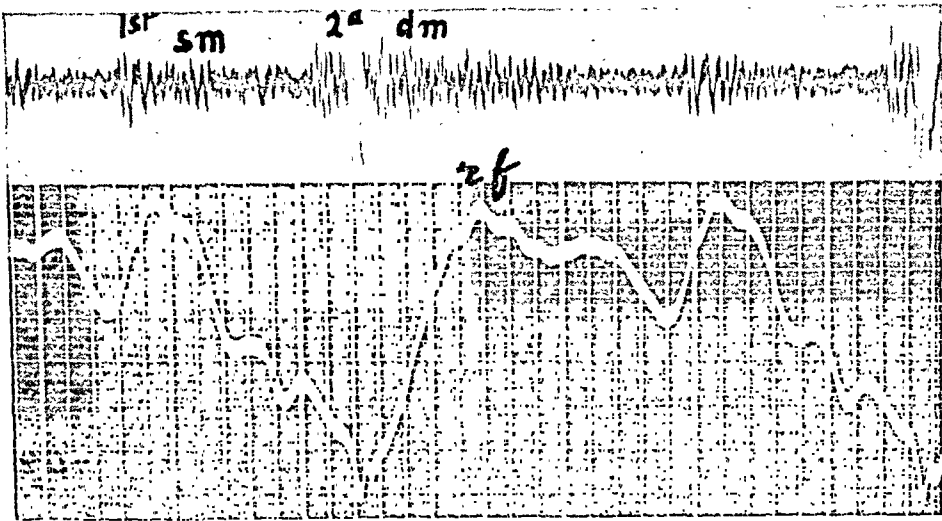


FIG. 4. Phonocardiogram and cardiogram recorded over the apex (Miller-White linear microphone). rf = wave of rapid filling of the ventricles; sm and dm—same as above.

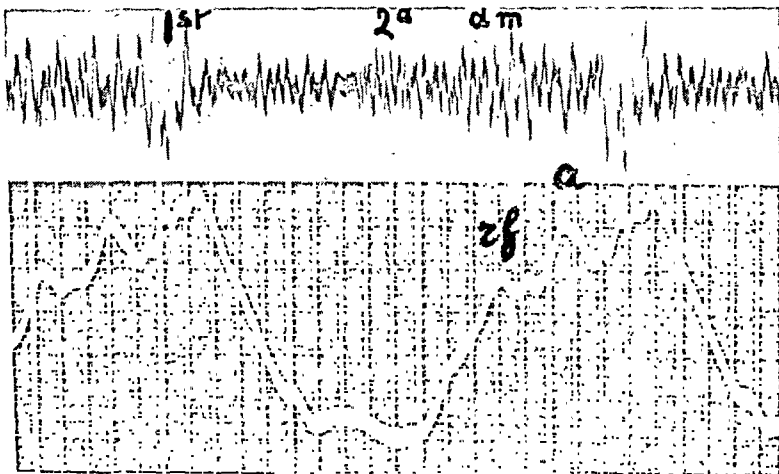


FIG. 5. Phonocardiogram and cardiogram recorded over the third left interspace. rf—same as figure 4; a = auricular wave of the cardiogram.

#### DISCUSSION

It is to be particularly noted that examination at the time of admission revealed no cardiac abnormalities. There can be no question, then, that in this case one is dealing with a true case of acute bacterial endocarditis, that is, duration under six weeks.<sup>3</sup> In 1939 Fletcher and Scott,<sup>4</sup> in reporting four cases of gonococcal endocarditis treated with sulfanilamide with recovery in one of these, comment upon the rarity of recovery in proved cases of gonococcal endocarditis.

They further add that if "one is extremely exacting in the criteria for establishing the presence of endocarditis and demands first, the culture and adequate identification of the organism (gonococcus in their cases) from the blood, and secondly, the presence of a diastolic murmur at the base of the heart emanating from the aortic or pulmonic valve and appearing or disappearing under observation, then there are only three reported cases of recovery." These criteria have been established in this case. In the same year Orgain and Poston<sup>5</sup> reported the recovery of a case of gonococcal endocarditis following treatment with sulfapyridine. Several authors<sup>1, 4, 5</sup> have commented on the somewhat more favorable prognosis in gonococcal endocarditis in general. Galbreath and Hall<sup>6</sup> in 1943 reported 67 cases of bacterial endocarditis at the Charity Hospital, New Orleans. Forty-two of these cases received therapy with one or more sulfonamide drugs. The diagnosis was based upon either (1) a compatible clinical picture plus one or more positive blood cultures or (2) necropsy evidence. These authors made no attempt to differentiate between acute and subacute forms of the disease. All of their cases died. Guerra<sup>7</sup> in 1943 reported recovery in two cases of hemolytic streptococcal endocarditis, which resulted from puerperal septicemia, following the use of penicillin. Dawson and Hobby,<sup>8</sup> in a discussion of the clinical use of penicillin, record three cases of acute pneumococcal endocarditis which were refractory to sulfonamide therapy and which were later treated with penicillin. Death occurred in all three cases, but it was later recognized that the dosages employed in their cases had been totally inadequate.

With the advent of drugs effective in the treatment of acute bacterial endocarditis the incidence of aortic regurgitation due to this condition will undoubtedly increase. The clinician must take this fact into consideration in establishing the etiology of this valvular defect which at present is almost always restricted to syphilitic or rheumatic infections.

#### SUMMARY

The term endocarditis is defined. A case of acute bacterial endocarditis is presented in detail. The literature is discussed briefly.

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SUBACUTE BACTERIAL ENDOCARDITIS, *STREPTOCOCCUS VIRIDANS*, WITH MESENTERIC THROMBOSIS  
AND RECOVERY \*

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CASE REPORT

*Present Illness.* The patient was a 25 year old white male, admitted to the hospital June 19, 1944, with a history of illness for the preceding five to six months. He stated that about five months previously he had had an acute mild attack of sinusitis, which persisted for about one week but cleared up after drainage. At about this time he began to have night sweats, which increased in intensity so that about the end of one month he had to get up two or three times each night to change clothing. At this time he began to notice weakness, anorexia, and vertigo. A month or two after this he began to have mild pain and swelling affecting knees, ankles, elbows, wrists, fingers and toes; this had persisted up to the present. The patient also had had one or two attacks of rather sharp pain in the left chest, which would persist for two or three days at a time. There had also been a rather persistent cough recently and for the preceding five or six weeks some swelling of the ankles and feet each afternoon, which would disappear by the following morning. At the onset of this illness the patient had had a diarrhea, which would return at intervals and then subside spontaneously, and which had recurred off and on for the preceding several months. The patient stated that on several occasions since the onset of all of these symptoms he had decided to seek medical advice, but that each time he made an appointment with the doctor he would feel a little better and cancel the appointment, so he had had no examination since the onset of this illness.

The presence of a congenital cardiac defect was discovered several years previously in the course of the patient's application for life insurance for which he was rejected. The patient had had no symptoms referable to his heart up to the present time, though he had known since this insurance episode of the presence of a murmur.

*Past History.* The patient had had scarlet fever at the age of 7, with no apparent residuals; also the usual childhood diseases. He was known to have had congenital kyphosis of the thoracic spine. The history otherwise was irrelevant.

*Physical Examination. General Appearance:* The patient was a fairly well developed, somewhat undernourished man, 25 years of age, who appeared acutely ill, and who exhibited a marked pallor. Temperature was 100.4° F., the pulse was 105 with occasional extrasystoles; blood pressure was 120 mm. Hg systolic and 40 mm. diastolic, the respirations, 22. Head was rather flat and square shaped. The eyes were slightly hyperopic; vessels normal. The nose contained mucopurulent exudate above middle turbinate. The teeth were in satisfactory repair. The throat was normal.

*Heart* was slightly enlarged, the apex impulse 9 cm. from midsternal line in fifth intercostal space. The heart border was about 3 cm. from midsternal line on the right from the third to the fifth interspace. There were blowing systolic murmurs at both apex and base and also diastolic murmurs over the whole precordium. The diastolic murmur was loudest over the aortic area. The pulmonic second was the only definite sound that was heard, and it was of a slapping quality. Rate was approximately 105 with occasional extrasystoles. Systolic murmur was transmitted to axilla and into the neck; there was a thrill over the left second interspace. *Lungs:* Diaphragm was high, because of a kyphosis; breath sounds were somewhat intensified; there were no

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areas of dullness, and no râles. *Abdomen*: The liver was felt just below the costal margin; the spleen was tender and palpable two fingers' breadth below the costal margin in the anterior axillary line; no fluid wave. *Spine*: There was a marked kyphosis. *Skin* showed marked pallor; no petechiae. *Extremities* showed slight clubbing of fingertips. *Impression*: subacute bacterial endocarditis superimposed on congenital heart disease.

*Course in the Hospital*: Penicillin 12,500 units i.m. every two hours was begun after the blood culture was reported positive for *Streptococcus viridans*. Within 24 hours after beginning penicillin, the patient's septic temperature disappeared and relatively normal temperature persisted from June 25 to July 5. The patient received two transfusions of 500 c.c. of whole blood, the second of which caused appreciable pulmonary congestion. In view of the apparent danger of producing cardiac failure, further transfusions at this time seemed inadvisable. The patient continued to improve and regain his strength, and night sweats completely disappeared two days after beginning penicillin. On July 2 and 3 the patient got out of bed and walked around the hall, against the doctor's orders, owing to the fact that he said he felt too well to stay in bed. On July 6 he was apparently normal until about 7 p.m., when he suddenly developed a sharp stabbing pain in the left upper quadrant, which in the course of about 15 minutes became very severe and caused frequent emesis. He was given donnatal and amphojel without relief; at 10 p.m. he was given pantopon, gr. 1/3; at 12 p.m., 4 a.m. and 8 a.m., an hyoscine-morphine compound no. 1; all of which gave only moderate relief. On examination at this time he showed a very tender and rigid abdomen, with marked tenderness in the left upper quadrant below the costal margin. The pain shifted in the next 24 hours, until it was about at the level of the junction of the left upper and left lower quadrant. An electrocardiogram on July 7 showed moderate change from one taken on June 19. Flat plate of the abdomen showed no definite signs of obstruction, but auscultation of the abdomen revealed an absolutely quiet abdomen with no peristalsis. Surgical consultation was called and exploratory operation was decided against owing to lack of a definite diagnosis and the patient's general condition. That day the patient began to show distention and, following a barium enema, a Levin tube was introduced with Wangenstein suction; also a rectal tube was inserted. This gave only moderate relief. The following day severe pain, nausea and vomiting persisted and no peristalsis could be detected. That day a Miller-Abbott tube was inserted and after 24 hours was started into the jejunum; the bag was inflated and in the next 24 hours was carried into the lower ileum. This relieved his distention and pain, although he was still very weak. In attempting to move himself on to a roentgen-ray plate one night he became markedly cyanotic. Fluids were given by subcutaneous route daily. On July 11 he was started on a high caloric liquid diet, to be taken by mouth if tolerated, and fruit juices with dextrose through the tube. After a day or so, he began to take larger amounts orally and the clyses were discontinued. On July 15, 50 c.c. of barium were introduced and passed through the tube satisfactorily showing that there was no obstruction. The tube was subsequently removed. Penicillin was discontinued on July 12 after he had had 5,475,000 units. Temperature at this time remained somewhat elevated, but not septic in type. The patient then pursued a rather uneventful course for several days until July 27 when he began to complain of pain in the heel and in the ball of the foot as "when he had the infection." At this time he also began to complain of pain in the left chest. On this date there was noticed some decrease in resonance and tactile fremitus at the left base. Within three days this progressed to an effusion in the left pleural cavity and a roentgenogram also showed a triangular area of increased density in the left lower lobe. Intercostal nerve block gave marked relief from pain. On July 30 a thoracentesis was performed and 300 c.c. of slightly xanthochromic serosanguineous fluid were removed. After thoracentesis the chest gradually cleared and no further untoward event occurred. The patient was very

gradually allowed to resume activity and was put on a maintenance dose of sulfathiazole tablets, two daily, which he was still taking at the time of this report.

*Laboratory Findings.* On admission hemoglobin was 40 per cent and red blood cell count 3,400,000. The last count done in the hospital showed 4,350,000 red blood cells and 80 per cent hemoglobin. The white cell count in the hospital fluctuated from 24,000 with 71 per cent polymorphonuclears at the time of the abdominal crisis to 10,000 with 70 per cent polymorphonuclears at the time of discharge.

Blood cultures showed a positive culture on June 21, with 100 colonies of *Streptococcus viridans* per 100 c.c. of blood.

Subsequent blood cultures on July 15, 19, 24, 29, August 6, 22, September 5 and 21 were all negative.

Urinalysis remained normal throughout the illness except for the occasional presence of small numbers of pus cells.

*Subsequent Course and Conclusion:* The acute abdominal episode was apparently due to a mesenteric thrombosis, occurring in the course of a subacute bacterial endocarditis, characterized by other embolic phenomena. This patient had, as noted in the history, recurrent joint disturbances, recurrent chest pain and cough, and one pulmonary infarct, which was demonstrable by roentgen-ray. The patient was extremely ill at the time of the abdominal crisis and the value of the Miller-Abbott tube, in this particular case, cannot be overestimated. It would certainly have been impossible to hope for successful results from any operative procedure on this individual, and there is no question but that the Miller-Abbott tube saved his life.

The patient was discharged on August 22, 1944 and at the time this report was being written, five months later, was still perfectly well.

*Note:* Appreciation is expressed to Dr. Lon Grove of Atlanta for his valuable assistance as a surgical consultant and for his suggestion and supervision of the use of the Miller-Abbott tube.

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## HYPERINSULINISM OF AN UNUSUAL TYPE: A METABOLIC STUDY \*

By JEROME W. CONN, M.D., F.A.C.P., MARGARET W. JOHNSTON, PH.D., and  
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WE report this case study of hyperinsulinism in detail because of its unusual character.

### CASE REPORT

*History.* On November 22, 1941 a 36 year old, white, unmarried, graduate nurse was admitted to the University Hospital for study. A diagnosis of spontaneous hypoglycemia, probably pancreatic in origin, had been made. The patient stated that her first episode of unconsciousness occurred on April 15, 1939 at a large eastern hospital where she was employed as a general duty nurse. Careful studies on the neurosurgical service revealed no intracranial cause for attacks of unconsciousness. A single determination of blood sugar at that time was recorded as 70 mg. per cent. In May 1939 she suddenly fell unconscious on a beach on the eastern seaboard. She was taken to a local hospital where "a very low blood sugar was found." A

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prompt return to her normal state was produced by the administration of glucose intravenously. During the next year attacks increased in frequency. She had been on night duty and it had been her custom to have breakfast and then to sleep through the lunch hour. She noted that upon awakening in the late afternoon she was frequently too weak to prepare food and on such occasions was likely to become unconscious. Except for occasional mild disorientation, nervousness and weakness there was no warning before attacks. There had been no convulsions of which the patient was aware. Hunger was not a prominent symptom, nor had it been noted that the ingestion of food would abort an attack. Attacks occurred at intervals of about three to five weeks. There had been a period of five months during which none had occurred.

The patient, in the interim, had moved to the South where detailed studies of her blood-sugar levels were made. A series of very low blood-sugar values was obtained during attacks and rapid relief was afforded by the administration of glucose. Values for fasting blood sugar, during periods when attacks were occurring, were reported as follows:

7/20/40—40 mg. %  
9/9/40—44 mg. %  
1/10/41—37 mg. %  
1/13/41—36 mg. %

Glucose tolerance test on July 23, 1940:

Fasting—71 mg. %  
½ hour—111 mg. %  
1½ hours—105 mg. %  
2½ hours—72 mg. %  
3½ hours—73 mg. %

Several tests had indicated normal liver function. There was no evidence to suggest organic disease of the pituitary, adrenals or central nervous system.

On May 8, 1941 one of us (J. W. C.) was consulted by mail and presented with the history and data given above. The opinion returned was that the data suggested "a pancreatic insulin-secreting tumor as the most likely cause of the hypoglycemia" and that they "afford a definite indication for careful and complete exploration of the pancreas."

The patient returned to the eastern hospital for operation. Shortly after admission on June 9, 1941 she lapsed into coma and was revived with the use of dextrose intravenously. The blood-sugar level during this attack was not determined. Over the next 10 days of observation no attacks occurred and frequent determinations of blood sugar revealed none to have been below 84 mg. per cent. On June 19, 1941 careful exploration of the abdomen revealed that the pancreas was firmer than normal. No tumor was discovered. Several specimens of pancreas were taken for biopsy. The patient had an uneventful postoperative convalescence and was discharged on July 6, 1941.

The biopsy specimens (figure 1) were interpreted as follows: "The general structure of the pancreas is altered by a slight diffuse increase in connective tissue and by an extensive infiltration of cells. Although interlobular connective tissue is but little increased, the slight intralobular fibrosis is clearly abnormal. The acinar cells are normal.

"The islands of Langerhans are normal in number, size and shape.

"The infiltration of cells mentioned is diffuse and intralobular. The cells are not acinar or connective tissue and do not appear inflammatory. They are probably

island cells and are so regarded. Among these the presence of both alpha and beta cells is suspected and further efforts are being made to demonstrate this.

"The Diagnosis: Slight pancreatic fibrosis. Normal islands with diffuse island cell hyperplasia."

Five weeks after discharge she was readmitted because of a return of attacks. On admission the blood sugar was 14 mg. per cent. Intravenous glucose restored her to normal consciousness. The blood sugar was entirely normal for the next four days and the patient was asymptomatic. She was discharged but was brought back 10 days later. Attacks occurred in the hospital with blood-sugar levels of 6 and 11

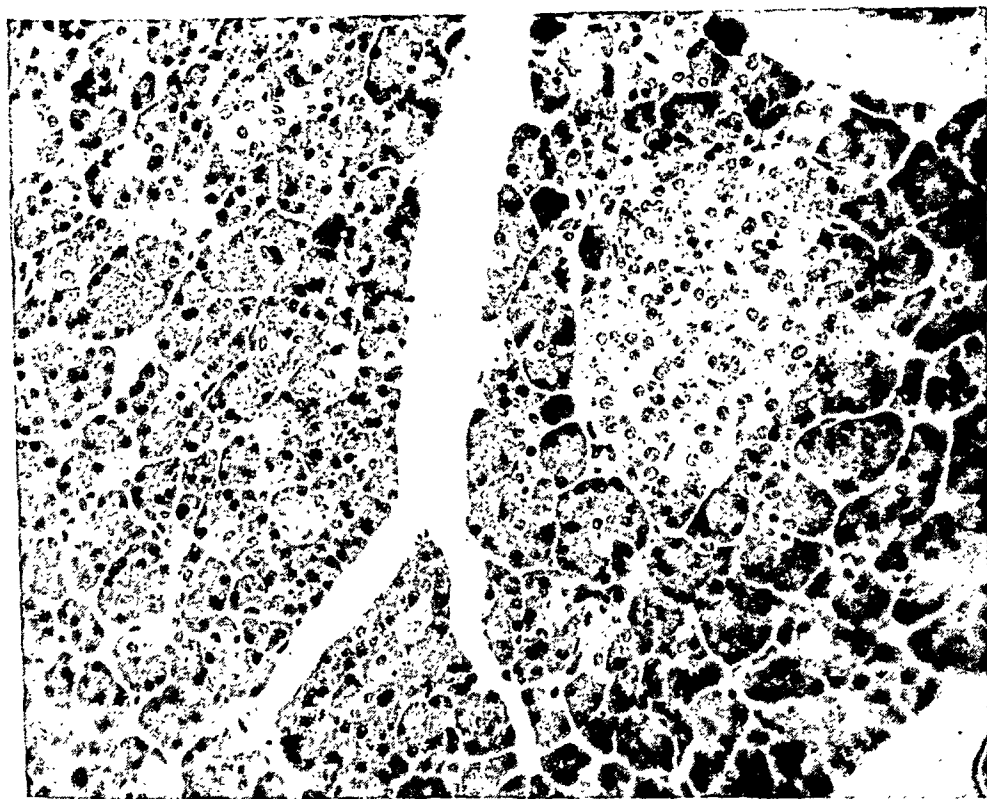


FIG. 1.

mg. per cent. During this period there were several spells of coma from which she recovered without glucose and during which the blood sugar was 91 and 93 mg. per cent.

The final opinion was that the patient was suffering from organic hyperinsulinism of an unusual variety and that the attacks which occurred with normal blood-sugar levels were probably psychogenic in origin.

In September 1941 the patient returned to the South where the attacks began to increase in frequency. By early November they were occurring almost daily. We were advised of the status and agreed that the question of partial or subtotal pancreatectomy should be considered. The patient was accordingly admitted to the University Hospital on November 22, 1941.

Her past health had always been good. At the age of 13 she was burned on the face and extremities with lye; at 21 she had undergone an appendectomy; in June 1938, in an automobile accident, there had been injury to the head with loss of consciousness for a few minutes with no obvious sequelae.



*Chronological Protocol of Studies (November 22, 1941 to January 26, 1942)*

- 11/22/41 10:00 a.m. Admitted to ward. Physical examination essentially negative except for multiple burn scars on face and extremities. Mentally lethargic with peculiar intermittent blank stare.
- 11:40 a.m. Slumped to floor from chair. Pallor, tachycardia, profuse sweating. Blood sugar 8 mg. per cent. 10 c.c. of 50 per cent glucose intravenously. Complete recovery within five minutes. Now very coöperative. No longer lethargic.
- Diet begun (2200 cal.—80 gm. P, 300 gm. CHO, 87 gm. F.).
- 11/23/41 8:00 a.m. Fasting blood sugar 85 mg. per cent. Feels well.
- 11:45 a.m. Blood sugar 90 mg. per cent. No symptoms all day.
- 11/24/41 8:00 a.m. Fasting blood sugar 70 mg. per cent. No symptoms.
- 11:50 p.m. Comatose. Blood sugar 65 mg. per cent. 10 c.c. of 50 per cent glucose intravenously. Recovery in two minutes.
- 11/25/41 8:00 a.m. Fasting blood sugar 70 mg. per cent. No symptoms.
- 4:40 p.m. Collapsed on floor beside bed. Blood sugar 95 mg. per cent. 8 c.c. of 50 per cent glucose intravenously. Immediate response.
- 11/26/41 8:00 a.m. Fasting blood sugar 66 mg. per cent. No complaints throughout the day.
- 11/27/41 8:00 a.m. Fasting blood sugar 75 mg. per cent. No complaints.
- 10:20 a.m. Fell to floor. No pallor, sweating, etc. Extremities warm. Occasional flutter of upper eyelids. Seems to be "faking." Severe supraorbital pressure administered. Quickly recovered. No glucose given. Feels well. Blood sugar during "attack" 83 mg. per cent.
- 11/28/41 8:00 a.m. Fasting blood sugar 65 mg. per cent. Glucose tolerance test begun
- |         |          |
|---------|----------|
| 1 hour  | 90 mg. % |
| 2 hours | 75 " "   |
| 2½ "    | 73 " "   |
| 3 "     | 74 " "   |
| 3½ "    | 73 " "   |
| 4 "     | 74 " "   |
- 4:30 p.m. Collapsed on floor. Blood sugar 95 mg. %. 10 c.c. normal saline intravenously. Relief in one minute.
- 11/29, 11/30, 12/1/41 Fasting blood sugars 75, 69, and 68 mg. per cent respectively. No attacks.
- 12/3/41 7:00 a.m. Placed in calorimeter<sup>1</sup> for metabolic studies. 7:00 a.m. to 9:00 a.m. equilibrium period.
- 9:00 a.m. Patient drank test dose of glucose solution at given signal. Continuous sampling from 9:00 a.m. to 1:00 p.m.
- 1:00 p.m. Removed from calorimeter. Blood sugar 68 mg. per cent. No attacks during this day.
- Note: Data indicate unusually high R. Q.'s as compared with normal controls under the same conditions (table 1, experiment 1).
- 12/4/41 Changed from high to low carbohydrate diet. Formula now 1200 cal., 50 gm. P, 20 gm. CHO, 102 gm. F. No attacks.

TABLE I  
Combustion of Carbohydrate, Fat and Protein  
by Standard Calculation of Respiratory Quotients.  
(Four Hour Test Periods in Calorimeter)

Experiment No.	Subject	Preparatory Diet (5 days) Maintenance Cal.		Test Dose in Chamber Glucose	Total R. Q.	Non-protein R. Q.	Total Heat Produced	Heat Produced Non-Protein	Source of Non-protein Calories %	
		Carbo-hydrate	Protein						CHO	Fat
I	Patient	Gm. 300	Gm. 80	Gm. 60	1.026	1.091	Cal. 209	Cal. 169	CHO 100	Fat 0
	*Organic hyper-insulinism	300	80	60	0.956	0.992	267	220	97.6	2.4
	Control	300	80	60	0.848	0.857	291	246	53.1	46.9
	Control	300	80	60	0.863	0.876	282	237	59.5	41.5
	Control	300	80	60	0.874	0.887	342	293	63.1	36.9
	Control	300	80	60	0.841	0.846	378	341	49.3	50.7
II	Patient	300	80	0	0.792	0.790	209	173	29.9	70.1
III	Patient	300	80	0	0.788	0.785	215	178	28.1	71.9
	*Organic hyper-insulinism	300	80	0	0.868	0.882	250	211	61.5	38.5
	Control	300	80	0	0.807	0.809	309	250	36.5	63.5
	Control	300	80	0	0.797	0.796	294	235	32.0	68.0
	Control	300	80	0	0.787	0.785	392	337	28.1	71.9
	Control	300	80	0	0.803	0.803	397	338	34.5	65.5
IV	Patient	300	80	40	0.935	0.954	193	171	85.3	14.7
V	Patient	300	80	40	0.920	0.940	216	187	80.7	19.3

\* Included for comparison. Proved case similarly studied \* with complete recovery after removal of islet cell adenomas.

Experiment I—Unusually high respiratory quotients.

Experiments II and III—Normal *final* respiratory quotients. See figure 2 for comparison of initial respiratory quotients.

Experiments IV and V—Very high R.Q.'s. Note that R. Q. values are higher than those of normals receiving a larger test dose of glucose (60 gm.).

12/5/41 8:00 a.m. Fasting blood sugar 75 mg. per cent.

3:30 p.m. Collapsed on floor. Blood sugar 83 mg. per cent. No physical signs of hypoglycemia. Roused spontaneously in 30 minutes.

10:00 p.m. Fell out of bed. Cannot be aroused. Blood sugar 95 mg. per cent. No treatment. Roused spontaneously in 15 minutes.

12/6 and 12/7/41 Fasting blood sugars 68 and 69 mg. per cent respectively. No symptoms.

12/8/41 8:00 a.m. Fell on floor. Blood sugar 82 mg. per cent. No treatment. Spontaneous recovery in 30 minutes.

12/9/41 8:00 a.m. Fasting blood sugar 64 mg. %

Glucose tolerance test:

1 hour	218 mg. %
2 hours	263 " "
2½ "	204 " "
3 "	110 " "
3½ "	41 " "
4 "	48 " "

No attacks throughout the day.

*Note:* This glucose tolerance response is to be expected of normal people who, previous to the test, have been eating a diet low in carbohydrate.<sup>2</sup>

12/10/41

Changed to high carbohydrate diet—2200 cal., 300 gm. CHO, 80 gm. P, 87 gm. F. No attacks.

12/11/41

No attacks.

12/12/41 3:30 p.m.

"Unconscious" in bed. Blood sugar 97 mg. per cent.

12/13/41 and 12/14/41

No attacks.

12/15/41 7:00 a.m.

Another calorimeter study, this time in the fasting state without a test dose of glucose.

1:00 p.m. Removed from calorimeter. Blood sugar 97 mg. per cent.

*Note:* Data show unusually high initial fasting R. Q. followed by a rapid fall (table 1, experiment 2 and figure 2, experiment 2).

UNUSUAL PATTERN OF RESPIRATORY QUOTIENTS

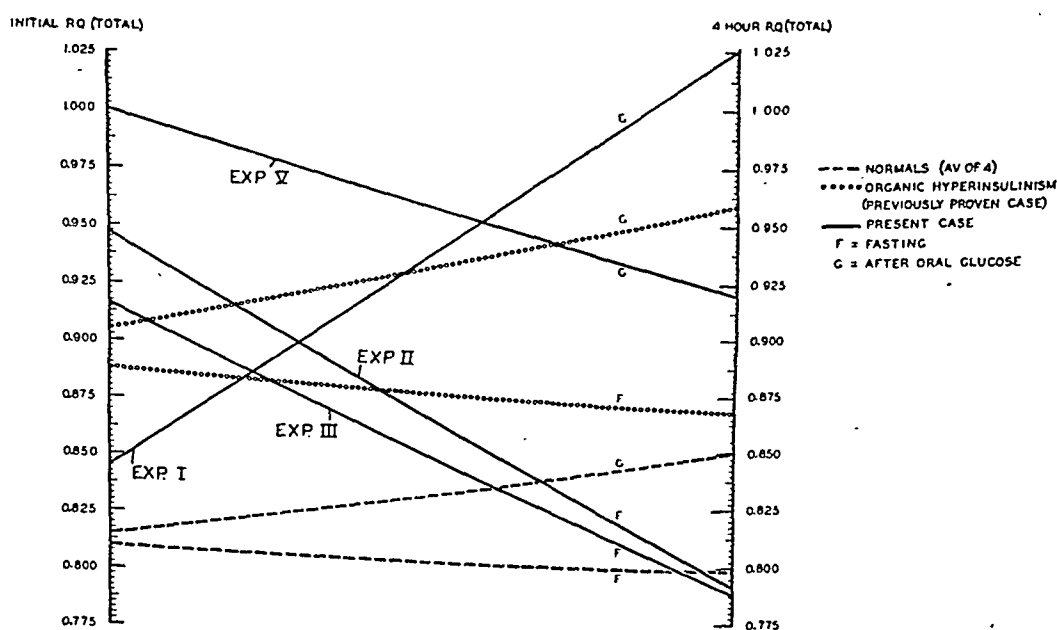


FIG. 2.

12/16/41

No attacks.

12/17/41

7:00 a.m. Repeated experiment of December 15, 1941.

1:00 p.m. Removed from calorimeter. Blood sugar 92 mg. per cent.

*Note:* Same result. Very high initial fasting R. Q. with rapid fall (table 1, experiment 3 and figure 2, experiment 3). Breakfast omitted. Blood sugar specimens obtained every half hour (9:00 a.m. to 1:00 p.m.) in attempt to explain peculiar data obtained in calorimeter.

12/18/41

Results: 9:00 a.m. .... 78 mg. %  
 9:30 a.m. .... 82 mg. %  
 10:00 a.m. .... 80 mg. %  
 10:30 a.m. .... 88 mg. %  
 11:00 a.m. .... 88 mg. %

11:30 a.m.	90 mg. %
12:00 a.m.	88 mg. %
12:30 a.m.	88 mg. %
1:00 p.m.	90 mg. %

No attacks.

12/19/41

No attacks. Slept most of the day.

12/20/41

Fasting blood sugar 80 mg. per cent. Has been extremely drowsy all morning.

*Note.* The head nurse was told in confidence to watch the patient's activities carefully. Suspicion had been aroused that the patient might be giving herself periodic injections of insulin. Reasons for suspicion were:

1. *Capricious clinical course.* Previous experience has taught us that in true organic hyperinsulinism one finds a fairly constant and predictable course of the blood sugar throughout the 24 hour period when the patient is taking a constant diet,<sup>3</sup> that a diet low in carbohydrate invariably produces severe hypoglycemia.<sup>4</sup> These expected findings were not observed.

2. *A psychogenic element undoubtedly present.* The attack which occurred two hours after admission to the hospital was hypoglycemic in nature (blood sugar 8 mg. per cent). In a great majority of the subsequent attacks the blood sugar was normal. Relief by intravenous glucose, intravenous saline, supraorbital pressure or by neglect indicated that at least some of the episodes were of a psychogenic nature.

3. *The unusual metabolic data.* The finding of extremely high respiratory quotients in the fasting state at 9:00 a.m. followed in the next four hours by an extremely rapid fall in the R. Q. was unexplainable in the light of our previous experience with normals and with organic hyperinsulinism (figure 2, experiments 2 and 3).

Had this extremely high R. Q. (observed in fasting state at 9:00 a.m.) been present throughout the night, very low levels of the fasting blood sugar should have been found. This was not the case. There seemed to be no explanation for a sudden increase in R. Q. while the patient remained in the fasting state unless: 1) she had surreptitiously ingested carbohydrate food; 2) she had hyperventilated with a resultant 'auspumpung' of CO<sub>2</sub> or 3) she had administered insulin to herself. Possibilities 1 and 2 were ruled out, but the third remained.

4. *Reevaluation of previous periods of hospitalization.* Our suspicions having been aroused we scrutinized the case summaries obtained from other hospitals and quote the following: May 8, 1941 (before operation) "Blood sugars taken immediately upon entrance during these episodes have always been below 40." June 9, 1941 (before operation) "Upon her arrival here from the train she went into a period of coma and was revived with the aid of glucose intravenously." For 10 days thereafter "the blood sugar did not fall below 84." August 12, 1941 (after operation) "The periodic development of symptoms led to two short admissions. On the first of these (August 12) her blood sugar was 14 on admission; 93 the next day and after four days without symptoms she was discharged." August 25, 1941 (after operation) "She had several attacks near the hospital entrance, a short time before she left for \_\_\_\_\_." On one occasion we obtained a blood sugar of 6 mg. per cent."

It should be recalled that the same pattern occurred on admission to our hospital, i.e., an episode of coma two hours after admission with a blood sugar of 8 mg. per cent.

12/21 and 12/22/41

No attacks.

12/23/41 7:00 a.m.

Placed in calorimeter.

1:00 p.m.

Removed from calorimeter. Results show again markedly elevated R. Q.'s. (table 1 and figure 2, experiment 4).

12/24/41 4:40 p.m. Unconscious on floor beside bed. Blood sugar 80 mg per cent.

*Note.* During this period bedside belongings of patient were investigated. There was no evidence of luer, needle or insulin! Wrapped in toilet paper, however, were found nine tablets of Nembutal. The physical form of these tablets was of the type dispensed only at this institution. This seemed to indicate that patient was actually taking things from the nursing station medicine cabinet.

After investigation, the head nurse reported that several partially used bottles of insulin had disappeared from the nursing station cabinet in the preceding two weeks. The nurse was instructed to check the insulin supply, but to leave the cabinet unlocked; she was asked not to arouse the patient's suspicions by search.

12/25/41 Christmas day. No attacks. Very depressed.  
12/26/41 4:00 a.m. Can't be aroused. Perspiring profusely. Thready pulse. Blood sugar 16 mg. per cent. Large amounts of glucose by vein and by stomach tube. Stuporous for two hours before recovery.

11:15 a.m. Unconscious. Blood sugar 85 mg. per cent. Continuous infusion of 5 per cent glucose begun.

12:30 p.m. Blood sugar 115 mg. per cent. Much better now.

12/27, 12/28, 12/29/41 No attacks.

12/30/41 7:30 a.m. Placed in calorimeter.

9:00 a.m. Signal given to drink glucose solution. The patient stared blankly through the window of the calorimeter. Movements were slow and uncoordinated. There was marked pallor. After a sharp command the patient managed to drink the glucose solution (40 grams glucose). There was marked coarse tremor of the hands.

9:30 a.m. Reacted normally again.

1:00 p.m. Removed from calorimeter. Staring expression again. Uncoordinated. Blood sugar 23 mg. per cent.

*Note:* Results show again markedly elevated R. Q.'s (table 1, experiment 5).

12/31/41, 1/1, 1/2/42 No attacks.

1/3/42 12:00 Midnight. The patient was observed going to the medicine cabinet twice. After the second visit, she was followed to the bathroom. When an attempt was made to take from her something wrapped in a handkerchief the patient hurriedly flushed it down the toilet.

A new, marked bottle of "U80" insulin was missing from the cabinet!

9:30 a.m. Unconscious, sweating profusely. Blood sugar 12 mg. per cent. She was carefully examined. Three new puncture wounds on anterior aspect of thighs were noticed. Intravenous glucose were administered, with prompt recovery. The patient was detained in the treatment room while a search was made for the insulin bottle.

A 5 c.c. luer and two hypodermic needles were found hidden in the bedside table. One needle was of a type not dispensed in this hospital. The luer and needles were replaced in the bedside table. After a two hour search, the missing marked bottle of "U80" insulin was found wrapped in toilet paper on a shelf in the women's lavatory. One hun-

dred twenty units had disappeared since the disappearance of the bottle the preceding night. All insulin remaining in bottle was removed, and an equal volume of typhoid "H" antigen (clear solution) was substituted. The bottle was rewrapped and replaced in its hiding place. The patient was told that important study in the calorimeter had been scheduled for the following morning.

*Note:* It seemed from the data that insulin had been taken shortly before each calorimeter study.

The patient slept well.

- 1/4/42      7:00 a.m. The patient was placed in the calorimeter. A hurried trip to the ward disclosed a deficiency of 3 c.c. of typhoid "H" antigen! (equivalent to a disappearance of 240 units of insulin, had the bottle contained its original substance.)
- 8:30 a.m. The patient had a chill in the chamber. Her face was flushed. She was removed from the chamber and returned to the ward.
- 10:00 a.m. White blood cells 6,400. Temperature 98° F. Pulse 120.
- 2:00 p.m. White blood cells 20,000. Temperature 101° F. Pulse 110.
- 6:00 p.m. White blood cells 15,000. Temperature 100° F. Pulse 95.

*Examination:* There was a large, hot, ecchymotic area, three inches in diameter, on the upper lateral aspect of the right thigh, with a puncture hole in the center. Very little importance was attached to this finding in the presence of the patient. She was allowed to hear of her fever and leukocytosis and probably thought she had taken an infected injection. We do not believe she suspected our discovery.

- 8:00 p.m. The typhoid antigen was replaced with distilled water and the bottle was returned to its hiding place. The medicine cabinet was locked.

- 1/5/42 thru 1/25/42 Eight "attacks" during which lowest blood sugar was 74 mg. per cent. The distilled water disappeared from the bottle in 1 to 2 c.c. amounts and finally the bottle disappeared, also.

- 1/26/42      2:00 p.m. The patient was found on the floor. There were three superficial linear cuts over the right jugular vein, with very mild bleeding. Scissors, with dried blood on the blades, were found under the bed. All instruments of possible injury were removed and the patient was confined to bed. She was conscious but refused to respond, lying flaccidly in bed.
- 3:30 p.m. The patient was again found on the floor, with profuse bleeding from a new, deep, linear gash one inch above the previous ones. No instrument was found. A pressure bandage was applied. The patient was transferred to the Department of Psychiatry.

#### COMMENTS REGARDING THE RESPIRATORY DATA

*I. Unusual pattern of respiratory quotients in present patient* (figure 2 and table 1). A comparison of the respiratory quotients of normal controls and of true hyperinsulinism (proved at operation) indicates precise similarity in the pattern of response during fasting or following ingestion of glucose. The outstanding difference lies in the fact that in organic hyperinsulinism the metabolic processes are going continuously at an abnormally high level of respiratory

quotient. This suggests a continuous supply of an abnormally large amount of insulin.

On the other hand, a glance at the initial respiratory quotients obtained in the present case convinces one that something of an erratic nature is going on. That for experiment 1 falls close to the normal range whereas the other three are very high. All three initially high quotients fell rapidly in the next four hours whether the patient remained in the fasting state or had received glucose orally. In experiment 1, where the initial quotient appeared normal, there occurred after the ingestion of 60 gm. of glucose, a very unusual rise in R. Q. to 1.025 at which level one must conclude at least some degree of conversion of carbohydrate to fat (this situation is discussed below). Having proved that the patient had been taking insulin, it now becomes easier to explain the unusual quotients. It is likely that the first time she was put in the respiration chamber (experiment 1) she took her injection of insulin shortly thereafter and while in the chamber. In the subsequent experiments she undoubtedly took the insulin several hours before she was taken down to the respiration chamber. She had been forewarned the evening before each experiment that she was to be taken to the calorimeter at 7:00 a.m. the next morning.

*II. The relationship between insulin activity, respiratory quotients and conversion of carbohydrate to fat.* In the classical interpretation of the non-protein respiratory quotient the non-protein heat production (as determined by the calorific value per liter of oxygen consumed at any given non-protein R. Q. between 0.7 and 1.0) is partitioned further into that amount of energy contributed by the oxidation of fat and that contributed by the oxidation of carbohydrate. Thus, at an R. Q. of 0.7 all of the non-protein energy is interpreted as having been derived from fat; at an R. Q. of 1.0 all from carbohydrate, at an R. Q. of 0.85, 50 per cent from each; and that by further interpolation the partitions of fat and carbohydrate can be arrived at for any R. Q. between 0.7 and 1.0.

It is agreed by all that a non-protein R. Q. in excess of unity (obtained under control conditions) indicates that conversion of glucose to fat has been occurring during that particular period of observation. It now becomes of interest to examine experiment 1 in detail. The four control subjects produced non-protein respiratory quotients ranging from 0.846 to 0.887. The patient with proved organic hyperinsulinism gave one of 0.992. The partition of calories for carbohydrate and fat (as calculated in the standard way) are given in table 1. The present patient, however, shows a non-protein R. Q. of 1.091. If one calculates the degree of conversion of carbohydrate to fat on the assumption that only that portion of the R. Q. above unity represents this process, one arrives at the following:

1. 13.9 gm. carbohydrate converted to fat.
2. 100 per cent of the non-protein calories derived from carbohydrate (44.6 grams).
3. No oxidation of fat.

Such an interpretation cannot be adequately defended, however, since it has not been demonstrated that all of the non-protein calories must be derived from the oxidation of carbohydrate before synthesis of carbohydrate to fat begins. Or to say it differently, it has not been shown that combustion of fat and synthesis of fat cannot go on simultaneously.

One could with equal justification, in the light of our present knowledge, suggest that all carbohydrate is first converted to fat at an R. Q. of 1.3 and that the fat thus formed is oxidized at an R. Q. of 0.7, the R. Q. resulting from this combination of events being in the region of 1.0.

Probably neither of these interpretations is entirely correct. It is likely that both direct oxidation of carbohydrate and the process of synthesis of fat from carbohydrate contribute to the rise in R. Q. following the ingestion of carbohydrate. At present, however, it is impossible to determine the extent to which each is contributory to the rise of the R. Q. under any particular set of conditions.

*Insulin Activity.* Of particular interest in this connection is experiment 1 (chart 2, table 1). Here the conditions of the experiment were identical with those of the controls, the one variable having been an injection of insulin of unknown quantity. Insulin activity has long been known to result in a rise of the non-protein respiratory quotient, and, by standard procedure, this rise has been attributed solely to the effect of the hormone in increasing combustion of carbohydrate. In experiment 1 the effect of insulin was certainly associated with a rise in R. Q. The effect, however, appears to have been sufficiently intense to have resulted in a R. Q. above unity. At least part of the total rise in R. Q., therefore, is due to synthesis of fat from carbohydrate and it appears to have been due to excessive insulin activity. In experiments 4 and 5 (with a smaller test dose of glucose) the R. Q.'s rose beyond those of the controls of group one (where a larger test dose of carbohydrate had been given). Although the quotients did not exceed unity it may properly be asked. "How much did the process of synthesis of fat from carbohydrate contribute to the rise obtained?" And finally the same question may be raised with regard to the normal controls.

Shoenheimer and his group<sup>5</sup> have shown, with the aid of isotopes, that adult mice of constant weight on a fat free diet synthesize fatty acids from carbohydrate and protein and simultaneously degrade an equivalent amount of fatty acids; that, in fact, there occurs within the space of five to nine days a replacement of half of the total body fatty acids by newly formed fatty acids, the source of the latter being in part, at least, carbohydrate.

The points discussed above (designed primarily to bring to the fore an element extremely disturbing to those who attempt interpretation of the respiratory quotient) are highly suggestive that the process of conversion of carbohydrate to fat contributes importantly to the rise of respiratory quotient obtained following administration of carbohydrate to normals; and that insulin activity is capable of intensifying this process.

#### SUMMARY

The case of a 36 year old woman with severe hyperinsulinism of three years' duration is described in detail. Careful exploration of the pancreas had failed to disclose a tumor. Biopsy of the pancreas revealed normal islands of Langerhans, but what appeared to be a diffuse intralobular type of pathology.\* The

\*Dr. F. D. W. Lukens of Philadelphia, who has kindly reviewed this manuscript, informs us that this type of intralobular change has been observed in human beings who have been asymptomatic during life.



clinical course was extremely bizarre. Metabolic studies and daily observations over a period of two months are recorded. The results clarify the unusual findings.

Comments are recorded regarding (1) the significance of respiratory quotients which exceed 1.0, and (2) the resulting implications in connection with interpretation of respiratory data generally.

*Follow-up Note.* Our patient insisted on leaving the Neuropsychiatric Institute (U. of M.) three days after her transfer to that unit and was turned over to her family. It was suggested that plastic surgery to her face might be of great value in bringing about social adjustment, but that psychiatric care was needed first; that surgery should not be attempted until a competent psychiatrist pronounced her ready for it.

After several poor attempts on her part, she finally became coöperative under the care of Dr. L. H. Twyeffort of Philadelphia, who kept us informed of her progress. On February 26, 1943, she finally admitted that she had consciously been taking insulin, but did not know "why she did it." She wondered whether, in addition, there might have been times when she had taken insulin with a later complete amnesia for her actions.

On October 26, 1943, Dr. Twyeffort wrote "Since March of this year (1943) she has successfully held a fairly responsible job at the University Hospital in town, and has been in charge of the central dressing room at night. . . . Also since that time she has been taking several extension courses at the Temple University night school and has now almost completed the high school credits which she was lacking. Her achievement record since last March I view as fairly encouraging against the background of her previous personality difficulties."

In the spring of 1944 and again in September, 1944, the patient had partial plastic repair of her face. General improvement was remarkable.

Sonenthal<sup>6</sup> has recently called attention to similar types of disturbances in nurses.

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## ECTODERMOSIS EROSIVA PLURI ORIFICIALIS (KLAUDER'S SYNDROME) \*

By NATHAN SILVER, Capt., M.C., A.U.S.

ABOUT 37 cases of Klauder's syndrome (ectodermosis erosiva pluri orificialis) are reported in the literature. This condition was described by Klauder of Pennsylvania in 1937. Since then there have been reports from various parts of the United States. That this condition is a rarity is evident by the sparsity of reports in the literature. Because of its rarity this case is thought worth reporting. However, since it presents itself in an evacuation hospital in an active theater of operations, the literature on hand is limited.

### CASE REPORT

Condition on admission: The patient was a 23 year old male who had been in the Army 22 months. On November 1, he was brought to the hospital acutely ill stating that for the four days prior to admission he had a slight sore throat, sore mouth, fever, and chills. Two days prior to admission he had developed a slightly productive cough, the sputum being odorless and not tinged with blood. His arms and legs ached slightly and he had a slight frontal headache. He had no chest pains, no cardiac, gastrointestinal, genitourinary, or joint complaints.

Family history was irrelevant. The only illnesses he had had in the past were chickenpox and measles in childhood. He did not think that he had lost any weight since being in the Army, his usual weight being 140 pounds.

Physical examination: He was an acutely ill male with a temperature of 102.8° F., pulse 116, respirations 30, blood pressure 110 mm. Hg systolic and 66 mm. diastolic. His pupils reacted normally to light and accommodation. No nystagmus was present. The sclerae were slightly injected. Sinuses were not tender. His lips showed marked herpes. The throat was injected but no exudate or membrane was present. No lymph nodes were palpable anywhere in the body. The heart was normal. His lungs revealed diminished resonance, distant breath sounds, with inspiratory râles in the left lower lobe. No pectoriloquy was present. The rest of the lungs were normal. The abdomen revealed no abnormalities. Liver, spleen and kidneys were not palpable. Five small papules each measuring two millimeters in diameter were present on the skin of the abdomen. Extremities showed no abnormalities. Reflexes were physiologic and no plantar responses were normal.

Course in the Hospital: Two days after admission a thick diffuse membrane, grayish and glistening in color, formed over the buccal mucous membrane, palates, uvula, fauces, pharynx, tongue and gums. This membrane was continuous and stripped with ease, leaving no bleeding surface. It was continuous with the membrane which had formed over both lips (figure 1). Only a small part was stripped off to see whether it would leave a bleeding surface. The extensiveness of the membrane persisted for six days and then for a period of five days gradually receded first from the buccal mucous membrane, then the gums, the pharynx, and finally the dorsum of the tongue. However, on the under surface of the tongue the membrane persisted and was still slightly present on discharge from the hospital 23 days after admission.

The lesions on the abdomen which were but five in number on admission, and were considered at that time to be insignificant, increased in number. For six days new crops appeared, involving the abdomen, chest, back, face, arms, thighs, legs, and

\* Received for publication February 24, 1945.

feet in that order (figure 2). None appeared on the soles of the feet and the palms of the hands. A few lesions appeared in the scalp. These lesions all went through a definite cycle, appearing first as small macules, then small papules, which became vesiculated. These vesicles had sloping edges with a clear fluid in them. The areola about the vesicles became larger. The vesicles then underwent hemorrhagic changes



FIG. 1. Shows the thick membranous exudate over the lips, a small portion of which has been stripped away. There are a few cutaneous lesions present.

and the areola became larger and more violaceous. The hemorrhagic center became crusted and the areola about it irregular and purplish in color. All the lesions went through the above changes, though when full grown the lesions varied in size. These hemorrhagic crusted forms persisted for seven days, the crusts then falling off and the areola about gradually fading in color. Only a small area devoid of epithelium

thus remained. These gradually healed over a period of days. On discharge from the hospital only a few crusted lesions remained on both legs and feet. The various stages in the development of these lesions are shown in figure 3.

On his third hospital day large subconjunctival ecchymoses appeared, covering all of the sclera of both eyes and these persisted for five days when absorption began. Absorption was slow and on the twenty-third hospital day only a small area remained in the right eye. He had no accompanying lacrimation but did complain occasionally of slight itching.

On the fourth hospital day the patient complained of burning on urination. Examination of the urethral meatus at that time revealed no evident erosion. However,

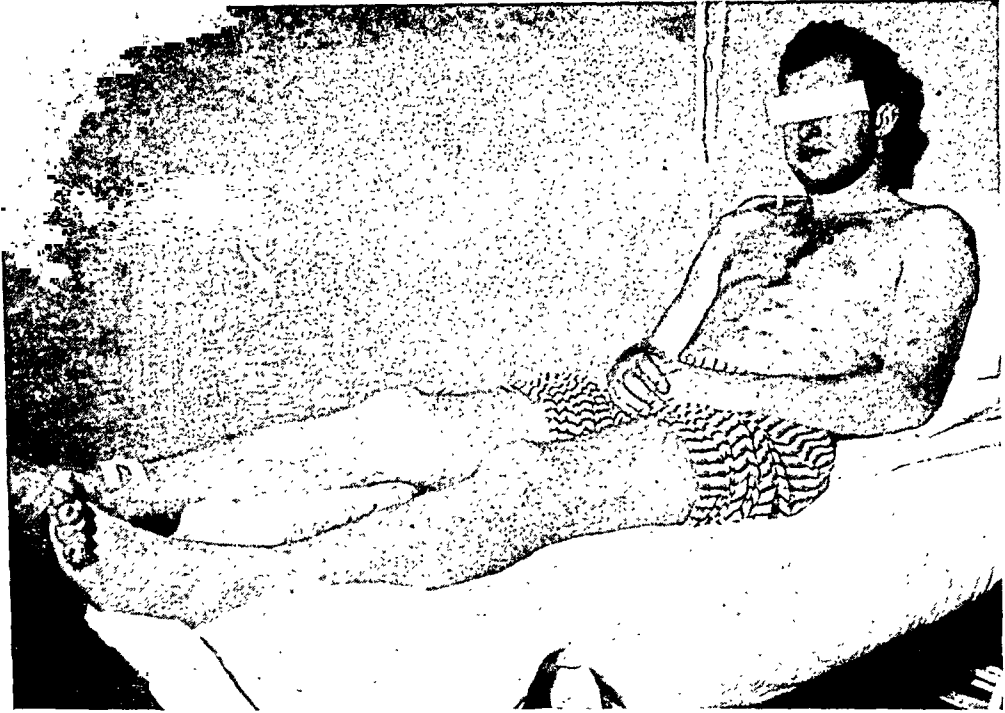


FIG. 2. Shows the distribution of the cutaneous lesions on the face, trunk and extremities.

on reëxamination of the urethral meatus 12 hours later small erosions were present (figure 4). These increased in extent for four days then gradually disappeared, so that five days later no erosion was present. At no time was a urethral discharge present.

On the fifth hospital day a small eroded area appeared about the anal orifice which increased in extent for three days then gradually healed so that no erosion was present nine days after its appearance.

The lungs which on admission revealed an atypical left lower lobe pneumonia also underwent changes. On his fourth hospital day râles, impaired resonance, and diminished breath sounds were present in the right middle lobe. The breath sounds in the left lower lobe were clearer, but râles were still present. Roentgenogram of the chest on this day revealed infiltration of the right middle lobe with some clearing in the left lower lobe. On the eighth hospital day inspiratory râles and impaired resonance were audible throughout both lungs. A chest roentgenogram taken on that day revealed flocculent densities involving both entire lung fields with a centripetal type of distribution (figure 5). These râles persisted and another roentgenogram

of the chest was made on the fifteenth hospital day. Both lung fields at this time showed uniformly mottled densities. These, however, were much lighter than on the film taken one week previously. On the twentieth hospital day no abnormalities could be found. On the twenty-third hospital day another chest roentgenogram was made which was reported as negative.

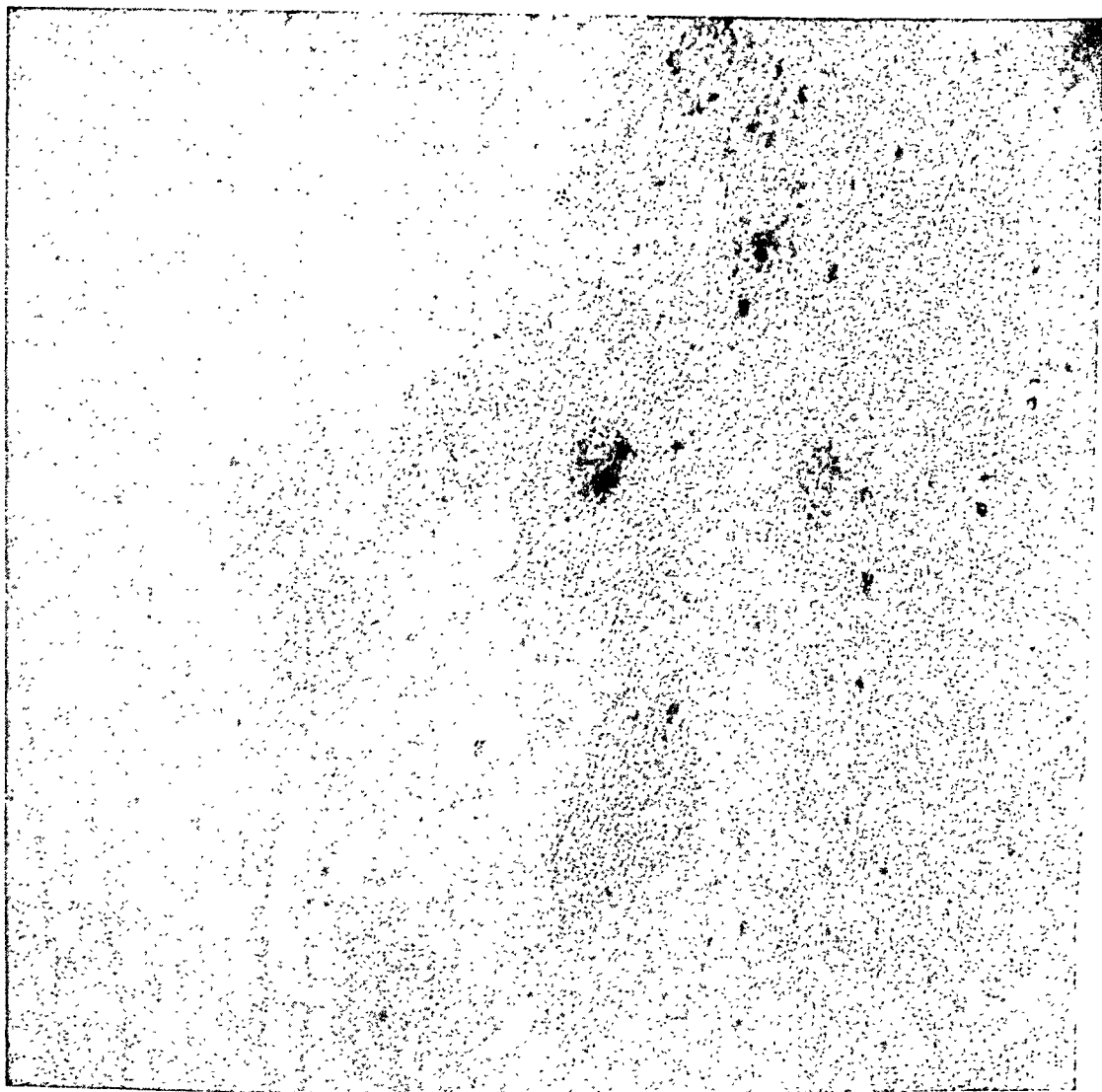


FIG. 3. Shows various stages in the evolution of the cutaneous lesions.

At no time were the spleen, liver, or kidneys palpable during hospitalization. Examination of the heart was always normal. For 11 days the patient's condition appeared critical. For two days, from the third to the fifth hospital days, the patient coughed up rather large amounts of blood-tinged tenacious sputum. Though his sputum was not measured a fair estimate was between one to two quarts of thick tenacious sputum a day.

From the third to the sixth hospital days the patient had three large episodes of epistaxis difficult to control. On the sixth and ninth hospital days the patient had two bowel movements, tarry and with streaks of red fresh blood. Thereafter his stools

were of normal color and consistency though frequent enemata had to be resorted to because of constipation.

His temperature for nine days ranged between 100° and 105.8° F., reaching a daily peak of at least 103° F. On the tenth hospital day his temperature for the first time was normal, with daily rises above normal. However, from the fifteenth hospital day a gradual decline in fever was present. The pulse and respirations followed the temperature so that an increase in temperature was accompanied by more rapid pulse and respirations.

*Laboratory Examinations.* Agglutination tests for typhoid "H" and "O," paratyphoid "A" and "B," undulant fever, OXK, OX2, OX 19, done on two occasions one week apart, were all negative. A mouth smear done on the second hospital day



FIG. 4. Shows erosions about the urethral orifice.

showed no predominating organisms. A throat smear done on that day was reported as showing no pathogens. On the ninth hospital day a throat culture was reported as showing non-hemolytic *Staphylococcus albus* and non-hemolytic streptococcus. On the ninth hospital day a culture of a vesicle on the leg was reported as showing no bacteria. Sputum examinations done on four occasions showed gram positive cocci occurring in pairs and short chains. No yeast or fungi were present on smear or culture. A culture of the sputum showed nonhemolytic *Staphylococcus albus* and gram positive bacilli which were not identified. Two blood cultures taken on the sixth and ninth hospital days were reported as showing no growth. The bleeding time done on the fourth and ninth hospital days was three minutes, 55 seconds, and two minutes respectively. Clotting time done at the same time was eight minutes, 20 seconds on the fourth day, and two minutes on the ninth day. Clot retraction was slight after eight hours. Reticulocyte count was 0.5 per cent. Platelet count on the ninth hospital day was 750,000 per cu. mm. A fragility test was normal, showing beginning hemolysis at .44 per cent and completion at .30 per cent, the control beginning at .42 per cent and completion at .30 per cent. Blood proteins and hematocrit were normal. His red blood cell count varied from 3,460,000 to 5,200,000 per cu. mm. of blood. Hemoglobin

ranged from 65 per cent to 80 per cent. For the first seven days of hospitalization the red blood cell count was below 4,000,000 per cu. mm. and the hemoglobin below 75 per cent. Thereafter both the red blood cell count and the hemoglobin were over those figures. The white blood cell count varied between 3,850 and 7,100 per cu. mm. The differential blood count showed polymorphonuclear leukocytes from 52 per cent to 80 per cent and the monocytes ranged from 4 per cent to 12 per cent. The rest were lymphocytes. Only a few non-filament forms were present and an occasional megalo-blast. Daily urine analyses were done and specific gravity ranged from 1.008 to 1.032.



FIG. 5. Roentgenogram taken in the eighth hospital day, showing flocculent areas of increased density over both lung fields, with a centripetal type of distribution.

From the second to ninth hospital days a trace of albumin was present. Otherwise the urine was entirely negative except for occasional red blood cells early in the illness. Sedimentation rates done on the third, ninth, and twenty-third hospital days were all increased. The readings were 38 mm., 72 mm., and 58 mm., in one hour respectively. Urinary output was from 1,500 c.c. to 2,000 c.c. daily.

The patient was treated with massive doses of thiamin chloride, nicotinamide, ascorbic acid, and vitamin K. He was given 1,890,000 units of penicillin in the first 10 days of hospitalization. Two small blood transfusions of 250 c.c. were given on the fifth and seventh hospital days. Plasma, 500 c.c., was given on the eighth day. Mapharsen, 0.03 gram, was given on the seventh hospital day and 0.06 gram on the ninth hospital day. The daily fluid intake was at least 3,000 c.c. using intravenous fluids if necessary.

The patient was discharged from the hospital on the twenty-third hospital day fully recovered, except for a small ecchymotic area in the right eye, and some crusted lesions on both lower extremities. The fact that there is some activity still present on discharge is evident by the rapid sedimentation rate. The patient lost 24 pounds in weight in the 23 days of hospitalization.

### SUMMARY

Klauder's syndrome is a disease involving the skin and mucous membranes of the body, the etiology of which is unknown. In six previous cases seen by one of my colleagues, pneumonia was present and probably is an integral part of the syndrome, although not described by Klauder. The disease runs a typical course presenting a definite sequence. Pneumonia and sore mouth are presenting findings. This is followed by the eruption on the skin of the trunk, later extending to the face and extremities. About the fifth day the urethral and perianal lesions occur. Bleeding from mucous membranes and subconjunctival ecchymoses are common. The appearance of the mouth is characteristic of the disease having the appearance of having had some powerful escharotic, as carbolic acid, applied. The extensiveness of the mouth lesions is seen in no other disease. The skin lesions, first macular, then papular, vesicular, increasing markedly in size, and then developing a hemorrhagic center, are characteristic of the disease. No pathogenic organisms have been recovered from these cases to explain the etiology of this disease.

As the etiology is unknown, there is no specific treatment. However, as it is known that the vitamins given have a specific beneficial effect on ectodermal and endodermal structures it would seem logical to use them. Since inability to swallow is evident in all cases, careful attention to the fluid balance is indicated, and fluids should be begun early. As protein intake is inadequate, some form of protein should be administered, if necessary intravenously. Since arsenic has been given in some cases, it was given in this case in the hope it would have some therapeutic value.

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## A CASE OF ATROPHIC TRACHEOBRONCHITIS WITH METAPLASIA \*

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THE occurrence of atrophic rhinolaryngotracheobronchitis is rare. Thompson<sup>1</sup> in 1926 defined atrophic laryngitis as a chronic inflammation of the mucous membrane resulting in atrophy and generally associated with the formation of crusts. It was his opinion that the condition resulted from purulent infections in the nose or accessory sinuses, ozena, syphilis, purulent catarrh or adenoids. In 1933, Hurd<sup>2</sup> described atrophic rhinitis as a disease which manifests itself in the upper respiratory passages with atrophy of the mucosa, crust formation,

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and fetor. Miller<sup>3</sup> in 1933 attempted to determine the frequency and etiology of atrophic laryngotracheitis and to differentiate the type secondary to nasal sinusitis from the rare type which follows nazal ozena. He concluded that primary laryngotracheitis is so rare that its existence is to be doubted and that atrophic laryngotracheitis and ozena of the trachea are to be considered synonymous. He was responsible for classifying atrophic laryngotracheitis into three varieties: (1) that with a thin pale mucous membrane with transparent cartilaginous rings, (2) pale atrophic mucous membrane studded with crusts with a metallic luster, (3) pale atrophic mucous membrane and the walls plastered with soft and dried crusts having a foul odor. All of these showed the pathological picture of metaplasia of columnar to stratified epithelium, fibrosis with chronic inflammation, atrophy of the mucous glands, and atrophy of the laryngotracheal perichondrium.

Marked keratosis of the upper respiratory tract associated with atrophic laryngotracheobronchitis has not been stressed. In 1938, New and Erich<sup>4</sup> reported 10 cases of keratosis of the larynx, two of which developed squamous cell carcinoma. These were cases of localized lesions and were not associated with atrophic laryngitis. In 1940, Morrison<sup>5</sup> reported a case in which epidermoid carcinoma of the larynx developed from a zone of keratosis in the subepithelial layer beneath the mucous glands. It was he who suggested that the most important detail of keratosis is a diffuse inflammatory lesion in the mucous membrane, but he failed to describe other associated findings.

Graham<sup>6</sup> in 1942 summarized his and previous observations on keratosis. He stressed that keratosis is a precancerous disease, that it is a localized cornification of the epithelium without invasion of the submucosa, and that there is a diffuse chronic inflammatory process throughout the mucous membrane with localized areas of intensity about the base of the lesions.

A search of the American literature revealed no combination of all the lesions which have been previously described; however, our case of longstanding atrophic rhinitis with ozena presented not only the typical gross findings of atrophic laryngotracheobronchitis but microscopic evidence of a combination of metaplasia of the epithelium with areas of ulceration, marked keratosis, hyperplasia of mucous glands, hypertrophy of the smooth muscle, increased connective tissue with chronic inflammation, areas of new bone formation in the submucosa, and degeneration of the cartilage.

#### CASE REPORT

T. J., a 40 year old, white male, was admitted to the Elizabeth Steel Magee Hospital on December 18, 1943 because of severe, almost intractable dyspnea, orthopnea, and a paroxysmal productive cough.

The patient gave a history of chronic rhinitis with crust formations and a fetid odor for 10 to 12 years. He had an intermittent postnasal drip with occasional expectoration of crusts. He was treated symptomatically at intervals, and he was never completely incapacitated by his chronic illness until early in 1942 when he developed dyspnea on exertion, paroxysmal attacks of dyspnea, and hoarseness. These symptoms gradually increased in severity necessitating admission to the Eye and Ear Hospital in September 1942. At that time he had marked atrophic rhinitis with thick crusts lining the entire nasal mucous membrane. A laryngoscopic examination showed

similar crusting of both vocal cords. Some of the crusts were removed. He was discharged after two weeks' observation and symptomatic treatment.

His symptoms remained partially abated, except for exacerbations brought on by several acute respiratory infections in the winter of 1942-1943, until the summer of 1943 when a marked increase in severity necessitated readmission to the Eye and Ear Hospital in September 1943. At this time laryngoscopic examination revealed atrophic vocal cords with much crusting. The crusts were removed with a biting forceps, and then a bronchoscopic examination was performed. The trachea showed numerous crusts, as did also the proximal portions of the bronchi. Most of these crusts were

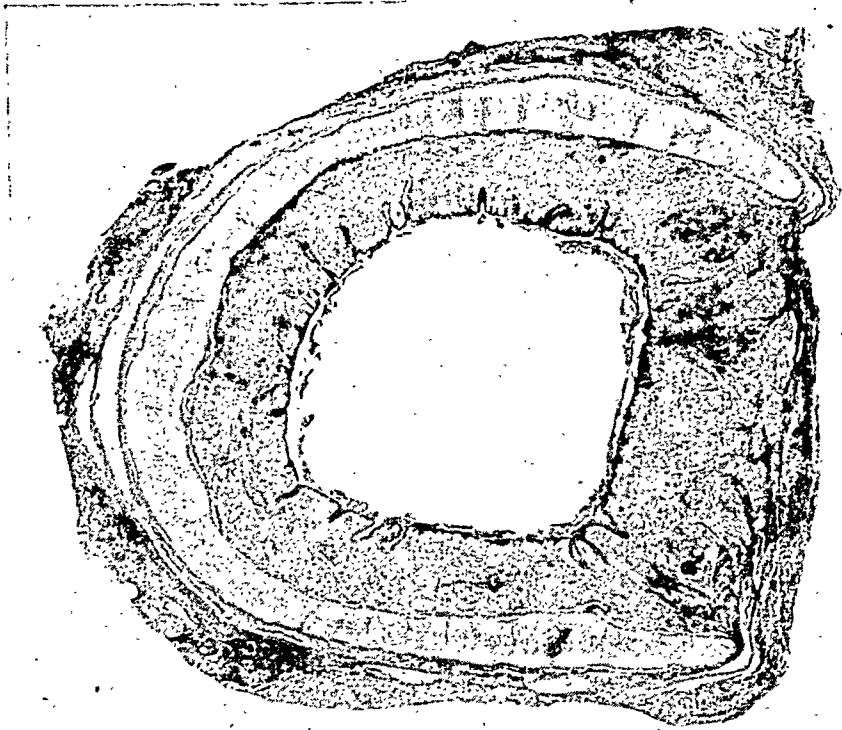


FIG. 1. Cross section of trachea just beneath larynx ( $\times 4$ ). The metaplasia of the columnar epithelium to stratified squamous epithelium is complete. Note the crypt-like extension of the epithelium into the underlying tissues. There is marked thickening especially between lining epithelium and the cartilage.

removed. Chest roentgenogram during this hospitalization showed no abnormalities, and other laboratory investigations were normal except for a two plus albuminuria. He was discharged in one week and experienced a marked relief of symptoms for several weeks. His symptoms again became progressively worse and were incapacitating. He was then referred to the Elizabeth Steel Magee Hospital.

His past medical history was non-contributory except in a negative way. He had no history of exposure to irritating vapors or dusts, no endocrine disease, and no nutritional deficiencies until just preceding the last hospitalization, when he ate poorly due to loss of appetite and aggravation of symptoms brought on by eating. There was no history of allergy.

Family history and personal history were non-contributory.

Physical examination on admission revealed a well-developed somewhat undernourished, white, middle-aged male with marked dyspnea and orthopnea. All acces-

sory respiratory muscles were active. The nasopharyngeal mucous membranes were atrophic. The nasal cartilage was deformed with resulting saddle-back nose. There were nine carious teeth and localized areas of gingivitis. In the midline of the soft palate was a scar from a previous cleft palate repair. The chest showed slight increase of anteroposterior diameter. The lungs were clear except for a few scattered crepitant râles and diminished breath sounds. The heart was normal. The blood pressure was 118 mm. Hg systolic and 78 mm. diastolic. The abdomen revealed no abnormalities. The extremities showed slight clubbing and cyanosis of nail beds. The skin was dry, somewhat thickened, and of poor tone.



FIG. 2. An area from figure 1 magnified 120 times. Note the stratified squamous epithelium with keratin and crusts. There is a chronic inflammation in the subepithelial connective tissue which is thick and collagenous.

During the hospital course, the patient's temperature varied between 98 and 99° F. There was a persistent tachycardia, 100 to 120 per minute. Respirations were always accelerated, and ranged from 25 to 60 per minute. Chest roentgenogram showed bronchial thickening in both lower lobes, especially in the right. All laboratory investigations were normal except for hypocholesterolemia and a persistent albuminuria. Serologic tests for syphilis were negative. Kidney function tests were normal. Arm to tongue circulation times were rapid. The vital capacity was moderately to markedly impaired, ranging from 1 to 2 liters. The patient had recurrent attacks of dyspnea with marked difficulty of inspiration. These were associated with coughing and were relieved by expectoration of tenacious sputum containing crusts. He was treated symptomatically and was given very large doses of vitamin A, as suggested by Wolbach and Howe's<sup>7</sup> work.

The recurrent attacks of dyspnea continued. On the twenty-fifth day of hospitalization, he had a severe attack of dyspnea which necessitated continued administration

of oxygen. After 12 hours he developed pulmonary edema which advanced rapidly, and he died 24 hours after the onset of severe dyspnea.

*Autopsy findings.* At autopsy the trachea was found markedly thickened, and the lumen just below the thyroid cartilage was considerably narrowed, measuring only 10 millimeters in diameter. On section, the mucosa of the trachea and primary bronchi was thickened and some areas were ulcerated and covered with dirty black crusts. The lungs were separated with ease and a small amount of straw-colored fluid was found in both pleural spaces. The lungs were red and wet, and a pink frothy fluid oozed from the bronchi. The other organs showed nothing unusual.

On microscopic examination the finding which we believe made this case of unusual significance was the complete metaplasia of the epithelium of the trachea just below the larynx (see figures 1 and 2). Here the epithelium was entirely of the stratified squamous variety with marked keratinization and irregular crusts extending into the lumen. These crusts were composed of keratin, debris, and bacteria. By means of the Brown-Brenn stain, gram-positive cocci in chains and in groups were found. The epithelium extended often as crypts into the underlying tissues. Beneath the surface epithelium, there was a low grade chronic inflammation including phagocytes filled with brown pigment. The smooth muscle was hypertrophied in places, and there were heavy islands of collagenous connective tissue. The mucous glands were involved in a dense chronic inflammatory reaction and showed degenerative changes. There were also degenerative changes in the cartilage. Actual bone formation had occurred in places between the surface epithelium and the mucous glands. The connective tissue was increased and was dense and collagenous. The wall from the lining epithelium to the cartilage was excessively thickened, as compared with a normal trachea.

Sections from the lower trachea and major bronchi revealed partial ulceration of the mucosa and scattered areas of metaplasia. The changes in the walls resembled those described in the upper trachea.

The lungs showed areas of congestion, consolidation, and collapse.

Other organs on microscopic examination revealed no significant abnormalities.

#### COMMENT

This case is introduced because it is both unusual and significant. It is unusual because it shows extensive pathological changes in the entire upper respiratory tract. These changes involve the entire wall of the respiratory tract including the proximal portions of the large bronchi. It is significant because (1) it indicates the relationship between chronic infections of the nose and chronic irritation of the lower respiratory passages with resultant decreased resistance and secondary infection, and (2) it stresses the relationship between chronic irritation and infection and precancerous lesions.

The clinical course during the patient's last period of hospitalization was of real interest. The lumen of the trachea was narrowed by the disease process resulting in moderate to marked dyspnea. When the lumen was further occluded by the presence of crusts, there was very marked respiratory embarrassment. This was relieved by a paroxysm of coughing which resulted in expulsion of the crusts. It was this blockage of the trachea which apparently resulted in pulmonary edema and death. The continued very deep inspiration resulted in an increased negative intrapleural pressure. As a result, fluid eventually entered the alveoli and lung interstitial tissue. This is the type of phenomenon observed by Drinker<sup>8</sup> in recent experiments. The rôle of vagal reflexes in the production of bronchospasm and saturation of the lungs must also be considered. Perhaps both played a part in this patient's death.

## CONCLUSIONS

1. A case of atrophic rhinolaryngotracheobronchitis is presented.
2. The complete squamous metaplasia of the epithelium of the upper trachea and associated pathologic findings in the tracheal wall make the case unusual.

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## EDITORIAL

### HEPATITIS

SINCE the outbreak of the war, hepatitis in the armed forces has presented a major medical problem, both for the United States and for many of the other nations involved, and it has been common in the civilian population in certain regions. The disease has appeared in two more or less distinct forms: infectious hepatitis, which includes at least a large proportion of the cases formerly termed "catarrhal jaundice," and "homologous serum jaundice," a hepatitis following the administration of human blood or blood products. The exact relationship of these two conditions is still in doubt.

Infectious hepatitis has an incubation period of about 30 days (in most cases from 20 to 40 days). Under war conditions it is often readily conveyed from one individual to another, and extensive epidemics have been reported. There is usually a prodromal period of a few days to two or three weeks, marked by fever which may reach 103° F., associated with chilly sensations, headache, malaise, marked fatigue, anorexia, digestive disturbances and abdominal discomfort or pain in the right upper quadrant. After a few days there may be a remission of the fever and symptoms, followed after a varying interval by a secondary rise in temperature, a recurrence of symptoms of greater severity and the appearance of jaundice. The jaundice usually reaches a maximum within a week and then slowly subsides, and with this there is amelioration of the symptoms. Jaundice usually disappears after two to four weeks, but may last for many months.

Many milder cases occur, without jaundice. Diagnosis of these cases may be difficult, but where there have been opportunities to study carefully large groups of individuals, it appears that the number of such cases exceeds those with frank jaundice. In other respects these cases are quite similar to those with icterus, except that the symptoms are usually milder and the evidences of impairment of liver function less marked.

Aside from the icterus, the principal abnormality on physical examination is enlargement of the liver, which may reach the crest of the ilium. The liver is tender, especially on fist percussion, and this may be one of the last manifestations to disappear. Barker et al.<sup>1</sup> have pointed out that there may be a latent period of several seconds before the pain is felt. There is tenderness in the right costovertebral angle. The deep inferior cervical lymph nodes on the right are often enlarged, and occasionally the spleen is palpable.

The urine is dark colored and contains bilirubin. The feces may be pale but contain some bile. The icterus index is high, the bilirubin in the serum is increased and yields an immediate positive direct van den Bergh reaction. There is no leukocytosis. There may be a lymphocytosis, with some ab-

<sup>1</sup> BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Chronic hepatitis, *Jr. Am. Med. Assoc.*, 1945, cxxix, 653-659.

normal cells resembling those seen in infectious mononucleosis, but heterophile agglutination tests have been reported negative. Special tests of liver function show impairment, especially the bromsulfalein excretion test (with or without jaundice) and frequently the cephalin cholesterol flocculation test. The alkaline phosphatase is often increased, and less regularly the serum globulin. In severe cases the prothrombin time is prolonged, and failure to respond to administration of vitamin K is a grave prognostic sign. The oral hippuric acid test has been reported as less satisfactory.

In a few instances the disease has been severe, with rapid development of intense jaundice, signs of acute liver failure, hemorrhages, delirium, coma and early death. The liver shows massive necrosis at autopsy. In milder cases, punch biopsies of the liver have shown milder degrees of degeneration and necrosis of liver cells, disintegration of cell columns, and cellular infiltration of the sinusoids and portal spaces, changes indistinguishable from those in 'serum jaundice.'<sup>2</sup> In other cases death may occur after a more protracted course of two or three months. The immediate mortality is relatively low, however, only 0.18 per cent in Barker's<sup>3</sup> series of 1172 cases studied in the Mediterranean theater.

In some cases symptoms disappear and recovery occurs rapidly with subsidence of the jaundice. In many, however, convalescence is protracted over a period of one to three months. Patients continue to complain of lassitude, easy fatigue, anorexia and gastrointestinal disturbances, and are intolerant of fat. They are intolerant of exercise, and of jolting, which is painful. Overactivity markedly increases the symptoms and may precipitate a severe icteric relapse. This tendency persists even after patients (while at rest) have apparently recovered. This point is stressed by Barker,<sup>3</sup> who devised a graduated exercise tolerance test as an aid in determining when recovery has occurred. Any recurrence of symptoms and particularly of liver enlargement and tenderness is regarded as indicating active disease and need for further treatment.

In a majority of the cases, substantially complete clinical recovery occurs within three months, although there is evidence that in some cases, special tests may show impairment of liver function for indefinitely long periods. In a smaller proportion of cases the disease may run a protracted chronic course. In Barker's series<sup>1</sup> of 431 cases carefully studied, 76 were still active four months after the onset of acute symptoms, 42 after six months and 8 after one year. Of these 33 finally recovered under observation. The outcome in the other cases was not known. Relapses were common in this group, sometimes with a recurrence of jaundice, and tended to be more protracted and severe than the original attack. In many cases the symptoms were relatively mild and uniform except as aggravated by exer-

<sup>2</sup> HAWLEY, W. L., et al.: Hepatitis following injection of mumps convalescent plasma. III. Clinical and laboratory study, with liver biopsy studies, *Lancet*, 1944, i, 818-821.

<sup>3</sup> BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Acute infectious hepatitis, Jr. *Am. Med. Assoc.*, 1945, cxxviii, 997-1003.

tion, intercurrent infection or alcoholic excesses. Persistent coarse tremors and marked vasomotor disturbances have been reported<sup>4</sup> (in postvaccinal hepatitis). A longer period of observation will be required to determine the incidence of cirrhosis in such cases, but it appears to be rare.

The active agent is present in the blood during the acute stage of the disease and for a period as yet undetermined prior to this.<sup>21</sup> It is present in the feces and has been reported in the urine and nasopharyngeal washings.<sup>5</sup> It passes through a Seitz filter that is impervious to bacteria and may therefore be regarded as a 'virus.' It is unusually resistant to heat, withstanding a temperature of 56° C. for 30 minutes. Study has been handicapped by the inability to transmit the infection to laboratory animals, necessitating the use of human volunteers. Although a few workers have reported its transmission to animals (pigs, canaries, chick embryos) this has not been confirmed. Recently, however, MacCallum and Miles<sup>6</sup> have reported the apparently successful transmission of the infection by serial inoculation in rats which had been on a diet designed to produce a mild degree of nutritional liver injury. Virulence for rats increased with successive passages. The agent was filtrable, and in one experiment passed through a 63 m $\mu$  Elford Gradocol membrane, indicating that the virus is relatively small.

The disease can be transmitted to man by parenteral injections of blood or plasma or filtered fecal extracts, and by feeding blood or feces or by spraying infected materials into the nasopharynx. There is strong epidemiological evidence that the disease is contracted under natural conditions by ingestion of food or water contaminated by infected feces. Kirk<sup>7</sup> has described an epidemic, presumably spread in this manner, occurring among New Zealand troops in a limited sector of the line at Alamein, in an area which had been contaminated by German troops suffering severely from the infection. Mechanical transmission of the virus by flies from infected excreta and cadavers was strongly suspected.

Neefe and Stokes<sup>8</sup> carefully studied an epidemic occurring in a children's summer camp in the North Eastern United States, in which 61 per cent of the population was infected in the course of a few weeks. Human volunteers were readily infected by oral administration of serum, feces, or Seitz filtrates of feces, but not by parenteral injections. They failed to produce infection with urine, nasopharyngeal washings or washings from trapped flies. Epidemiological evidence strongly suggested that the infection was spread by water from a camp well which presumably had been contaminated by drainage from neighboring cesspools. Four out of five volunteers who

<sup>4</sup> BENJAMIN, J. E., and HOYT, R. C.: Disability following post-vaccinal hepatitis, Jr. Am. Med. Assoc., 1945, cxxviii, 319-323.

<sup>5</sup> FINDLAY, G. M., and WILLCOX, R. R.: Infective hepatitis. Transmission by faeces and urine, Lancet, 1945, ii, 594-597.

<sup>6</sup> MACCALLUM, F. O., and MILES, J. A. R.: A transmissible disease in rats inoculated with material from cases of infective hepatitis, Lancet, 1946, i, 3-5.

<sup>7</sup> KIRK, R.: Spread of infective hepatitis, Lancet, 1945, i, 80-81.

<sup>8</sup> NEEFE, J. R., and STOKES, J., JR.: An epidemic of infectious hepatitis apparently due to a water borne agent, Jr. Am. Med. Assoc., 1945, cxxviii, 1063-1075.



later ingested considerable amounts of this water showed either clinical manifestations of illness, significant impairment of liver function or both, after an incubation period of about two months, although they did not develop jaundice. All four were later immune to infection as tested by feeding contaminated feces which produced the disease in seven of nine control cases.

They also showed that the virus retained its infectivity in water deliberately contaminated, after the latter had been subjected to the usual chlorination procedures or had been cleared with sodium carbonate and aluminum acetate. The ordinary methods of disinfecting water supply appear to be inadequate for elimination of this virus.

Infection from contaminated urine is also possible, and probably by droplet infection<sup>8</sup> (based on epidemiological evidence). Biting arthropods have been suggested as possible vectors, but there is no direct evidence to support this.

"Homologous serum jaundice" is a form of hepatitis which has followed the injection of human blood or plasma from individuals who showed no evidence of clinical disease and as a rule gave no history of jaundice or of an illness suggesting infectious hepatitis. As is well known, many such cases followed the use of certain lots of yellow fever vaccine which contained human serum. The earlier reports of this syndrome were reviewed in this journal in 1943.<sup>9</sup> The predictions which had been made at that time that similar cases of jaundice might be anticipated following the widespread use of plasma have been amply confirmed. Studies of such cases occurring in the American armed forces have been reported, among others, by Rappaport<sup>10</sup> and by Grossman et al.<sup>11</sup>

In its clinical manifestations, pathologic lesions and evidences of impaired liver function, the disease is practically indistinguishable from infectious hepatitis except for the long incubation period, 60 to 120 days (extremes of six weeks to six months) before frank jaundice appears. Neefe and Stokes,<sup>12</sup> however, in a group of inoculated volunteers, observed fever and relatively mild manifestations of illness without jaundice two to four weeks after inoculation, an interval corresponding to the incubation period of infectious hepatitis. This was followed by a remission, more or less complete, and later by the reappearance of symptoms of greater severity with (usually) jaundice, about 90 days after the inoculation. The immediate mortality is usually low, about 0.2 per cent, although in certain epidemics it has been considerably higher.

<sup>8</sup> Editorial: Hepatitis following the administration of human serum, *Ann. Int. Med.*, 1943, xix, 368-371.

<sup>10</sup> RAPPAPORT, E. M.: Hepatitis following blood or plasma transfusions, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 932-939.

<sup>11</sup> GROSSMAN, E. B., STEWART, S. G., and STOKES, J., JR.: Posttransfusion hepatitis in battle casualties and a study of its prophylaxis by means of human immune serum globulin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 991-994.

<sup>12</sup> NEEFE, J. R., STOKES, J., JR., et al.: Hepatitis due to the injection of homologous blood products into volunteers, *Jr. Clin. Invest.*, 1944, xxiii, 836-855.

The agent is present in the blood before and during the period of jaundice, and probably in the nasopharyngeal secretions.<sup>13</sup> The infectivity of feces has not been definitely determined. Transmission to animals has not been accomplished, but it is readily transmitted to human volunteers by parenteral injections. Minute amounts of serum—0.1 c.c. or less—suffice. It has also been transmitted by feeding serum, but less regularly. It passes through a Seitz filter and resists heating at 56° C. for 30 minutes.

Accidental transmission of serum jaundice by the use of dirty syringes has been reported by several British observers. Bigger<sup>14</sup> reported observations which indicated that postarsphenamine jaundice was not due to a toxic action of arsenic on the liver, but to the transfer of virus from one patient to another. MacCallum and Bower<sup>15</sup> have confirmed these observations. It has been shown that when blood is withdrawn by the usual method, some is sucked back from the syringe into the vein when the tourniquet is released. Traces of blood in a syringe which has been carelessly cleaned and not sterilized undoubtedly suffice to transmit the infection. Manifestly syringes as well as needles must be adequately sterilized for routine venepunctures.

The resemblance of this virus and the disease it produces to infectious hepatitis is so striking that many have concluded they are identical. If not identical they must be closely related. There are certain differences in behavior, however, which have not yet been adequately explained. One is the incubation period before the appearance of severe symptoms, which is three times as long in serum jaundice as in infectious hepatitis. There is no obvious reason why intravenous injection of the virus should so delay the course of the infection as compared with oral administration. They appear to differ in the readiness with which they are conveyed under natural conditions. Contact infections are not uncommon with infectious hepatitis, but occur rarely if at all with serum jaundice. Although both infections have been transmitted by the oral and parenteral routes, infectious hepatitis appears to be more readily and certainly transmitted by oral administration whereas the reverse is true of serum jaundice.

Tests for cross immunity between the two infections are limited in number and have not as yet yielded decisive results. Recovery from infectious hepatitis seems to be followed, at least temporarily, by a substantial degree of immunity.<sup>8</sup> Individuals who have recovered from serum jaundice have been reported resistant to reinoculation with this agent.<sup>16, 17</sup> Oliphant<sup>16</sup> reported that 10 volunteers who had recovered from serum jaundice were all resistant

<sup>13</sup> FINDLAY, G. M., and MARTIN, N. H.: Jaundice following yellow fever immunization. Transmission by intranasal instillation, *Lancet*, 1943, i, 678-680.

<sup>14</sup> BIGGER, J. W.: Jaundice in syphilitics under treatment, *Lancet*, 1943, i, 457.

<sup>15</sup> MACCALLUM, F. O., and BOWER, D. J.: Homologous serum jaundice. Transmission experiments with human volunteers, *Lancet*, 1944, i, 622-627.

<sup>16</sup> OLIPHANT, J. W.: Infectious hepatitis. Experimental study of immunity, *Pub. Health Rep.*, 1944, lix, 1614-1616.

<sup>17</sup> NEEFE, J. R., STOKES, J., JR., and GELLES, S. S.: Homologous serum hepatitis and infectious (epidemic) hepatitis: Experimental study of immunity and cross immunity in volunteers: A preliminary study, *Am. Jr. Med. Sci.*, 1945, ccx, 561-575.

to subcutaneous inoculation of serum from cases of infectious hepatitis, which produced the infection in four of 11 normal controls. Paul et al.,<sup>18</sup> however, reported the experimental transfer of infectious hepatitis to three volunteers who had recently recovered from serum jaundice and stated that there is little evidence that an attack of serum jaundice or catarrhal jaundice protects from infectious hepatitis. Recent observations of Neefe et al.<sup>17</sup> confirm this view. Six volunteers who had recovered from serum jaundice proved immune when reinoculated with this agent, although eight of nine controls were infected. When inoculated with the agent of infectious hepatitis, five of the six became infected, as well as five of six controls inoculated orally (but none of six other controls inoculated parenterally). The evidence at present, therefore, favors the view that the two agents are different, but further study is required to determine this point conclusively. If this view is correct, practically nothing is known as to the mode of spread of the virus of serum jaundice under natural conditions.

The number of individuals who are carriers or who have subclinical infections with the virus is not known, but is presumably small. The custom of pooling the plasma from many donors undoubtedly increased greatly the incidence of serum jaundice in the recipients. Not all individuals who receive infected blood contract the disease. In controlled experiments the number developing outspoken illness is about 40 per cent. Aside from tests on human subjects, there is no way of determining the presence of the virus. Since the mortality is low and recovery usually complete, blood or plasma should not be withheld when it is really needed.

There is no specific therapy available. Attempts have been made, however, to use "immune" gamma globulin, obtained from normal human plasma, to prevent or ameliorate the course of the disease. Favorable results have been reported by Gellis et al.<sup>19</sup> and by Havens and Paul.<sup>20</sup> It did not have curative value. In the case of serum jaundice, results have been conflicting,<sup>11</sup> and the value of the procedure is uncertain.

<sup>18</sup> PAUL, J. R., HAVENS, W. P., SABIN, A. B., and PHILLIPS, C. B.: Transmission experiments in serum jaundice and infectious hepatitis, *Jr. Am. Med. Assoc.*, 1945, cxviii, 911-915.

<sup>19</sup> GELLIS, S. S., et al.: The use of human immune serum globulin (gamma globulin) in infectious (endemic) hepatitis in the Mediterranean theater of operations. I. Studies on prophylaxis, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1062-1063.

<sup>20</sup> HAVENS, W. P., and PAUL, J. R.: Prevention of infectious hepatitis with gamma globulin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 270-272.

<sup>21</sup> Since this editorial was written, W. P. HAVENS, JR. (Period of infectivity of patients with experimentally induced infectious hepatitis, *Jr. Exper. Med.*, 1946, lxxxiii, 251-258) reported failure to transmit the infection with the serum of one patient in the "midincubation period." He was also unable to transmit the infection with pooled specimens of urine or nasopharyngeal washings from five patients during the acute stage, whose serum and feces were infective; or with serum or feces obtained 25 to 31 days after the onset of acute symptoms.

## REVIEWS

*The Osseous System. A Handbook of Roentgen Diagnosis.* By VINCENT W. ARCHER, M.D. 320 pages; 21 × 14.5 cm. Year Book Publishers, Inc., Chicago. Price, \$5.50.

As stated in the preface by the author, it is obvious that this book is intended for those who interpret films occasionally. A roentgenologist might find cause to criticize this volume as one for reference, but without doubt, the author has succeeded in his task. He has prepared a book which should be of distinct value to the occasional reader of films.

Starting with the fundamental aspects of roentgen ray diagnosis, Dr. Archer points out very clearly in the beginning the difference between good and poor films and how their character can be improved. He does not clutter his book with detail technical matter, but he does mention the usual causes for unsatisfactory films.

In natural progression, he briefly outlines the approach to interpretation of films. Unfortunately the all important subject of normal anatomy (roentgen) is presented in a rather sketchy form. Numerous good films are reproduced, of examples of trauma to the various bones. Associated with these injuries, he includes a discussion, as well as films, of diseases that simulate trauma but are not traumatic in origin. As he considers each bone, a brief but valuable paragraph is included which discusses technical factors affecting the bone under examination.

The latter two principal sections of his volume are divided between those diseases that affect the bones of children and those of adults. A new approach is used in reaching a diagnosis, for the diseases are listed or arranged according to which portion of the bone is involved. For example, those diseases which produce periosteal proliferation are grouped together; those that involve the joints constitute another group; neoplastic diseases are in still another group, etc. For one not accustomed to seeing large numbers of films this offers an obvious advantage. It is not necessary to look up many different diseases in order to determine which ones produce periosteal changes, since they are already discussed as a group.

The type is very readable and the reproductions are good. The majority are printed as negative films; positive reproductions serve more to confuse a diagnosis than to help. For those to whom this volume is directed, this handbook is recommended without qualification.

D. J. B.

*Electrotherapy and Light Therapy—with the Essentials of Hydrotherapy and Mechanotherapy.* Fifth edition. By RICHARD KOVACS, M.D. 694 pages; 24 × 16 cm. 1945. Lea and Febiger, Philadelphia, Pa. Price, \$8.50.

Modern physical medicine is presented with the clarity and word economy we associate with Dr. Kovacs.

One peak of interest discusses protection against radio interference from electrical apparatus. "Important activities of the Naval Research Laboratories at Washington, D. C. were subjected to interference so serious as to stop the work completely. Eventually the disturbance was traced to therapeutic equipment. The first disturbance was traced to therapeutic equipment. The first disturbing instrument located was a diathermy unit in a hospital at Cambridge, Mass." Short-wave sends out a considerable amount of radiation, uncontrolled and travelling far. Remedies are screening of short wave diathermy machines, or, allocation of a special band for therapeutic purposes. Full metallic sheathing of rooms in which short wave machines are housed is expensive and has not proved successful. Federal Communications Commission,

release No. 80502, May 17, 1945 gives the most recent information. On page 244 you find the combined administration of high and low frequency by use of a filtering device so that both currents may be delivered simultaneously to the patient from the same binding posts.

The contraindications to hyperthermy provoke thought. Patients with myocardial degeneration or with valvular, coronary or other cardiac abnormalities, with impaired renal function from organic disease, with excessively high blood pressure or arteriosclerosis or with tuberculosis, diabetes, or far advanced syphilis of the central nervous system (late, rapidly progressing cases or patients who are totally demented) do not tolerate such treatment well and should not be subjected to it. "Warren (Rochester, N. Y.) adds, chronic alcoholism, acute respiratory infections and those rendered susceptible to heat prostration by a lower salt intake during the summer months." Age limits preferred, two to sixty.

The chapter on electrical injuries deserves much emphasis to doctors, physical therapists and medico-legal experts.

Light and radiation, physics and technics reflect modern changes. "No old style hot quartz lamp should ever be placed directly over the patient's body." The dangers of medically unsupervised home treatments form a briefed noteworthy report from the Medical Society of the County of New York. Air-sterilization discussion closes the chapter.

Hypothermy and cold injuries form an interesting report with suggested refrigeration technics.

One wonders if authorities will ever agree on a table such as The Average Range of Joint Movements or does progress initiate itself among such diversities?

Landis and Gibbon's diagnostic test to determine how much dilatation of the vascular bed is possible is quoted.

Although the author apparently favors Sister Kenny's treatment of polio, he points out that thermotherapy may more suitably take the place of the expensive hot pack system, with a more definite estimate as to extent and length of heat dosage.

Polyclinic experts contribute chapters on genitourinary conditions, proctological conditions, dermatological conditions and ear, eye, nose and throat conditions. These express a wide and discerning appreciation of physical medicine.

A 14-page glossary covering electro-physics and muscle and nerve action terms is a thoroughly useful feature of this book.

G. E. S.

#### BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Pathology in Surgery.* By NATHAN CHANDLER FOOT, A.B., M.D. 511 pages; 26 × 18.5 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, \$10.00.

*Clinical Roentgenology of the Heart.* By JOHN B. SCHWEDEL, M.D. 380 pages; 26.5 × 20.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$12.00.

*Industrial Toxicology.* By ALICE HAMILTON, A.M., M.D. and RUTHERFORD T. JOHNSTONE, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D., F.A.C.P., Hon. F.R.C.P. (Can.). Reprinted from Oxford Loose-Leaf Medicine with same page numbers as in that work. 69 pages; original page numbers 597 to 663; 24 × 15.5 cm. 1945. Oxford University Press, New York.

*Contribuicao para o estudo do diagnostico clinico da lepra nervosa.* By OSWALDO FREITAS JULIAO. 203 pages; 23 × 16.5 cm. 1945. Biblioteca do S. P. L. Caixa Postal, Sao Paulo, Brazil.

*Valor Pronostico del Electrocardiograma.* By DR. MANUEL VELA. 336 pages; 24 × 17 cm. 1944. Libreria Editorial Cientifico Medica Espanola, Madrid.

*Insuficiencia Supra-Renal Paludica. Conceito de Disionia Paludica.* By DR. ATILIO ZELANTE FLOSI, Da Universidade de Sao Paulo, Brazil. 128 pages; 23 × 15.5 cm. Editora Renascenca, Sao Paulo.

*The Physiological Basis of Medical Practice.* By CHARLES HERBERT BEST, C.B.E., M.A., M.D., D.Sc., F.R.S., F.R.C.P. and NORMAN BURKE TAYLOR, U.D., M.D., F.R.S., F.R.C.S., F.R.C.P., M.R.C.S., L.R.C.P. 1169 pages; 26.5 × 17 cm. 1945. Williams and Wilkins Co., Baltimore. Price, \$10.00.

## CORRECTION

In the article, A Study of One Hundred Cases with a Positive Coccidioidin Skin Test, in the ANNALS OF INTERNAL MEDICINE, 1946, xxiv, 40-59 (January), by Lt. Colonel Dumont Clark and Lt. Colonel John H. Gilmore, several illustrations of the chest roentgenograms were misplaced.

The roentgenogram in figure 3 should be in figure 6.

The roentgenogram in figure 5 should be in figure 9.

The roentgenogram in figure 6 should be in figure 7.

The roentgenogram in figure 7 should be in figure 7A.

The roentgenogram in figure 7A should be in figure 3.

The roentgenogram in figure 9 should be in figure 9A.

The roentgenogram in figure 9A should be in figure 5.

The legends and schematic drawings are correctly placed in the article.

At the time proof was corrected, the authors were in Military Service and not readily accessible. We regret the error.

## COLLEGE NEWS NOTES

### NOMINATIONS FOR A.C.P. ELECTIVE OFFICES, 1946-47

In accordance with the By-laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1946-47, are herewith announced and published:

*President Elect* .....Hugh J. Morgan, Nashville, Tenn.  
*First Vice President* .....James J. Waring, Denver, Colo.  
*Second Vice President* .....A. B. Brower, Dayton, Ohio  
*Third Vice President* .....T. Homer Coffen, Portland, Ore.

The above nominations were presented one year ago, but due to ODT war regulations, no Annual Business Meeting of the College could be held. Consequently the current Officers remained in office for the additional year, and regular elections will take place at the 1946 Annual Session at Philadelphia, May 13-17. The Business Meeting will be held Thursday afternoon, May 16, in the General Sessions hall of the Philadelphia Municipal Auditorium.

The election of nominees shall be by the Fellows and Masters of the College. The above Nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-laws.

Respectfully submitted,

Francis G. Blake, New Haven, Conn.

Robert O. Brown, Santa Fe, N. M.

John H. Musser, New Orleans, La.

John W. Scott, Edmonton, Alta.

Walter W. Palmer, *Chairman*, New York, N. Y.

COMMITTEE ON NOMINATIONS

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### MEETINGS, A.C.P. COMMITTEE ON CREDENTIALS

Proposals of candidates for Associateship and Fellowship must be filed thirty days in advance of action by the Committee on Credentials. That Committee will meet April 14 and May 12. Action recommended by the Committee will be reviewed and acted upon finally by the Board of Regents at Philadelphia, May 12. Announcements of elections will be posted near the Registration Desk at the Philadelphia Municipal Auditorium on the opening day of the Annual Session, May 13.

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### THE VICTORY CONVOCATION

All Fellows elected since April 20, 1942, and all Fellows elected prior thereto who were not formally inducted, are urged to be present at the "Victory Convocation" at Philadelphia, May 15, 1946. The exercises will be held in the ballroom of the Benjamin Franklin Hotel. More than one thousand new Fellows are eligible for induction on this occasion. An impressive and dignified program has been planned.

## RETIREMENTS FROM SERVICE

Since the publication of February number of this journal, the following members of the College have been reported retired or on terminal leave from active military service:

Elbert Boogher Agnor, Atlanta, Ga. (Capt., MC, AUS)  
J. Heinz Ahronheim, Jackson, Mich. (Capt., MC, AUS)  
Carl Richard Ahroon, Jr., Bloomington, Ill. (Comdr., MC, USNR)  
Louie Edgar Allday, Dallas, Tex. (Lt. Comdr., MC, USNR)  
Edgar V. Allen, Rochester, Minn. (Col., MC, AUS)  
Kenneth Dayton A. Allen, Denver, Col. (Col., MC, AUS)  
Forrest Nelson Anderson, Los Angeles, Calif. (Maj., MC, AUS)  
Karl Frederick Arndt, Denver, Colo. (Capt., MC, AUS)  
Dudley Curtis Ashton, Beckley, W. Va. (Lt. Col., MC, AUS)  
Harold Cook Atkinson, Macon, Ga. (Maj., AUS)  
  
Frederick Randolph Bailey, New York, N. Y. (Lt. Comdr., MC, USNR)  
Gordon Wesley Balyeat, Grand Rapids, Mich. (Lt., MC, AUS)  
Maurice C. Barnes, Waco, Tex. (Capt., MC, AUS)  
Walter Bauer, Boston, Mass. (Lt. Col., MC, AUS)  
William Bennett Bean, Cincinnati, Ohio (Maj., MC, AUS)  
Julian Ruffin Beckwith, Clifton Forge, Va. (Capt., MC, AUS)  
J. Edward Berk, Philadelphia, Pa. (Maj., MC, AUS)  
James McRae Bethea, Memphis, Tenn. (Lt. Comdr., MC, USNR)  
Philip G. C. Bishop, New York, N. Y. (Lt. Col., MC, AUS)  
Lewis Blanton, Fairmount, W. Va. (Lt. Col., MC, AUS)  
Edward Ward Boland, Los Angeles, Calif. (Maj., MC, AUS)  
James Michael Bowers, Seattle, Wash. (Lt. Col., MC, AUS)  
Norton Sager Brown, New York, N. Y. (Comdr., MC, USNR)  
Heinrich George Brugsch, Waban-Newton, Mass. (Capt., MC, AUS)  
  
Orange Van Calhoun, Lincoln, Nebr. (Comdr., MC, USNR)  
Louie T. Carl, Jackson, Miss. (Maj., MC, AUS)  
Henry R. Carstens, Detroit, Mich. (Col., MC, AUS)  
Louis Joseph Cheskin, Newark, N. J. (Maj., MC, AUS)  
Richard Edward Ching, Memphis, Tenn. (Lt. Comdr., MC, USNR)  
Hunt Cleveland, Anniston, Ala. (Maj., MC, AUS)  
Ralph L. Coffelt, Waco, Tex. (Lt. Comdr., MC, USNR)  
Wilfrid Joseph Comeau, Bangor, Maine (Lt. Col., MC, AUS)  
Raphael Joseph Condry, Elkins, W. Va. (Lt. Comdr., MC, USNR)  
Charles Henry Conley, Jr., Buckeystown, Md. (Comdr., MC, USNR)  
Linn F. Cooper, Washington, D. C. (Maj., MC, AUS)  
William Philip Corr, Riverside, Calif. (Col., MC, AUS)  
William Llewellyn Cover, San Bernardino, Calif. (Lt. Comdr., MC, USNR)  
Felix Hughes Crago, Great Falls, Mont. (Maj., MC, AUS)  
Charles John Crawley, Brooklyn, N. Y. (Lt. Comdr., MC, USNR)  
Morgan Cutts, Providence, R. I. (Capt., MC, AUS)  
  
Donald Howard Daniels, Portland, Maine (Lt. Comdr., MC, USNR)  
Lowrey Frederick Davenport, Brookline, Mass. (Maj., MC, AUS)  
John Holmes Davie, Philadelphia, Pa. (Lt. Col., MC, AUS)  
John Preston Davis, Winston-Salem, N. C. (Maj., MC, AUS)  
Francis George Dickey, Baltimore, Md. (Lt. Col., MC, AUS)  
Francis R. Dieuaide, Boston, Mass. (Col., MC, AUS)  
Ira Dixson, Stockbridge, Mass. (Maj., MC, AUS)



Ellet Haller Drake, Lincoln, Nebr. (USPHS-(R))  
Charles Dennis Driscoll, W. Collingswood, N. J. (Col., MC, AUS)  
Earl Danford DuBois, Portland, Ore. (Lt. Col., MC, AUS)  
Charles Newton Duncan, Dallas, Tex. (Lt. Comdr., MC, USNR)

Franklin Gessford Ebaugh, Denver, Colo. (Col., MC, AUS)  
Robert Allison Edwards, Houston, Tex. (Capt., MC, AUS)  
Ralph Arthur Elliott, Gary, Ind. (Capt., MC, AUS)  
David Edwin Engle, Elmhurst, Ill. (Maj., MC, AUS)  
Eugene Charles Eppinger, Brookline, Mass. (Col., MC, AUS)  
Roberto Francisco Escamilla, San Francisco, Calif. (Maj., MC, AUS)

Theodore Richard Failmezger, Madison, N. J. (Lt. Col., MC, AUS)  
Henry D. Fearon, Brooklyn, N. Y. (Comdr., MC, USNR)  
John Buckley Fershtand, Fort Worth, Tex. (Lt. Comdr., MC, USNR)  
Harold Fink, Brooklyn, N. Y. (Comdr., MC, USNR)  
Maurice Fliaser, Jr., San Francisco, Calif. (Lt. Col., MC, AUS)  
Paul Kendrick French, Burlington, Vt. (Lt. Col., MC, AUS)  
Julian Maxwell Freston, New York, N. Y. (Lt. Comdr., MC, USNR)  
Maurice Harold Friedman, Chicago, Ill. (Maj., MC, AUS)  
Robert Abraham Frisch, Milwaukee, Wis. (Capt., MC, AUS)  
Marshall Nairne Fulton, Brookline, Mass. (Maj., MC, AUS)

John Edward Garcia, New Orleans, La. (Capt., MC, AUS)  
Edgar Gilmore Givhan, Jr., Birmingham, Ala. (Lt. Comdr., MC, USNR)  
Paul Mitchell Glenn, Cleveland, Ohio (Maj., MC, AUS) (Deceased)  
Rubin Leonard Gold, San Francisco, Calif. (Lt. Col., MC, AUS)  
A. Allen Goldbloom, New York, N. Y. (Lt. Col., MC, AUS)  
Philip Goldstein, New York, N. Y. (Col., MC, AUS)  
Harold Habich Golz, Clarksburg, W. Va. (Maj., MC, AUS)  
Percival Allen Gray, Jr., Santa Barbara, Calif. (Comdr., MC, USNR)  
Mervin Edward Green, Ann Arbor, Mich. (Maj., MC, AUS)  
George Smith Grier, III, Newport News, Va. (Capt., MC, AUS)  
Lewis Perkins Gundry, Baltimore, Md. (Maj., MC, AUS)  
Henry Beall Gwynn, Washington, D. C. (Lt. Col., MC, AUS)

Snowden Cowman Hall, Jr., Danville, Va. (Lt. Comdr., MC, USNR)  
Everett England Hammonds, Birmingham, Mich. (Maj., MC, AUS)  
Karl Boyles Hanson, Jacksonville, Fla. (Maj., MC, AUS)  
Maurice A. F. Hardgrove, Milwaukee, Wis. (Col., MC, AUS)  
Harold Ellsworth Hathhorn, Youngstown, Ohio (Lt. Col., MC, AUS)  
Lyle Everett Heavner, Detroit, Mich. (Lt., MC, USNR)  
Standiford Helm, Evanston, Ill. (Maj., MC, AUS)  
Max William Hemingway, Bend, Ore. (Lt. Col., MC, AUS)  
Howard Eugene Heyer, Chicago, Ill. (Lt. Col., MC, AUS)  
Robert Emmett Hobbs, Shenandoah, Pa. (Lt. Col., MC, AUS)  
Willard Fletcher Hollenbeck, Portland, Ore. (Lt. Col., MC, AUS)  
Arthur Julian Horton, St. Albans, L. I., N. Y. (Lt. Comdr., MC, USNR)

William Knowlton Ishmael, Oklahoma City, Okla. (Maj., MC, AUS)

Allen Sheppard Johnson, Springfield, Mass. (Lt. Comdr., MC, USNR)  
William Henry Kammerer, New York, N. Y. (Maj., MC, AUS)  
George Kaplan, Woodside, L. I., N. Y. (Lt. Col., MC, AUS)  
Samuel Russel Kaufman, Wilkes-Barre, Pa. (Lt. Comdr., MC, USNR)

Frederick Kellogg, Long Beach, Calif. (Lt. Col., MC, AUS)  
William David King, San Francisco, Calif. (Assistant Surgeon, USPHS)  
Henry Bingham Kirkland, New York, N. Y. (Maj., MC, AUS)  
Edward Caffron Klein, Jr., Newark, N. J. (Comdr., MC, USNR)

Oza Joseph LaBarge, New Orleans, La. (Lt. Col., MC, AUS)  
Richard Paul Laney, Skowhegan, Maine (Maj., MC, AUS)  
Frederick Louis Landau, Jr., Bronxville, N. Y. (Capt., MC, AUS)  
Robert William Langley, Los Angeles, Calif. (Lt. Comdr., MC, USNR)  
Joseph Levy, New Rochelle, N. Y. (Maj., MC, AUS)  
Bernard Isaac Lidman, Norfolk, Va. (Maj., MC, AUS)  
Robert Samuel Liggett, Denver, Colo. (Maj., MC, AUS)  
Frank B. Lusk, Chicago, Ill. (Col., MC, AUS)  
George William Lynch, Boston, Mass. (Comdr., MC, USNR)

Alec Cameron MacNiel, Cleveland, Ohio (Maj., MC, AUS)  
Isaac Hall Manning, Durham, N. C. (Capt., MC, AUS)  
Edward de Saunhac Matthews, New Orleans, La. (Maj., MC, AUS)  
Richard Francis McLaughlin, Price, Utah (Comdr., MC, USNR)  
Harold Hiques McLemore, Spokane, Wash. (Maj., MC, AUS)  
John Patrick McVay, Seattle, Wash. (Capt., MC, USNR)  
James Clayton Metts, Savannah, Ga. (Lt. Col., MC, AUS)  
Francis Ralph Meyers, Paterson, N. J. (Comdr., MC, USNR)  
Roscoe Frick Millet, Macomb, Ill. (Maj., MC, AUS)  
John Barnhart Morey, Ada, Okla. (Maj., MC, AUS)  
Willis A. Murphy, New York, N. Y. (Lt. Comdr., MC, USNR)  
Joseph Ennalls Muse, Jr., Baltimore, Md. (Capt., MC, AUS)

Robert Anton Newburger, New York, N. Y. (Capt., MC, AUS)  
John W. Norcross, Boston, Mass. (Lt., MC, USNR)

Alexander Pierce Ormond, Akron, Ohio (Lt. Col., MC, AUS)

Henry Felch Page, Philadelphia, Pa. (Comdr., MC, USNR)  
Russell Clarke Pigford, Tulsa, Okla. (Lt. Comdr., MC, USNR)  
Wallace Lamar Poole, Johnson City, Tenn. (Comdr., MC, USNR)  
Reno Russell Porter, Boston, Mass. (Lt. Col., MC, AUS)  
F. Kenneth Power, Salem, Ore. (Maj., MC, AUS)

Hilton Shreve Read, Atlantic City, N. J. (Lt. Col., MC, AUS)  
Elmer Shackelford Robertson, Richmond, Va. (Capt., MC, AUS)  
David Harry Rosenberg, Chicago, Ill. (Comdr., MC, USNR)  
Oscar Ferdinand Rosenow, Columbus, Ohio (Maj., MC, AUS)  
William Ward Rucks, Jr., Oklahoma City, Okla. (Lt. Col., MC, AUS)

John Paul Sauvageot, Akron, Ohio (Capt., MC, AUS)  
Maxwell Scharf, Philadelphia, Pa. (Capt., MC, AUS)  
Irwin C. Schumacher, San Francisco, Calif. (Col., MC, AUS)  
Louis Adrian Schwartz, Detroit, Mich. (Lt. Comdr., MC, USNR)  
Lamont R. Schweiger, Milwaukee, Wis. (Capt., MC, AUS)  
John Wherry Shadle, Butler, Pa. (Maj., MC, AUS)  
Henry I. Shahon, West Roxbury, Mass. (Maj., MC, AUS)  
Lloyd Webster Sheckles, Jr., Galveston, Tex. (Lt. Col., MC, AUS)  
William Marco Sheppe, Wheeling, W. Va. (Capt., MC, USNR)

Harry Willard Shuman, Rock Island, Ill. (Capt., MC, AUS)  
 Roger Graham Simpson, San Francisco, Calif. (Maj., MC, AUS)  
 Lauren Howe Smith, Philadelphia, Pa. (Col., MC, AUS)  
 Howard Burnham Sprague, Chestnut Hill, Mass. (Capt., MC, USNR)  
 Frederick Steigman, Chicago, Ill. (Lt. Comdr., MC, USNR)  
 Leonard Gerard Steuer, Cleveland, Ohio (Lt. Col., MC, AUS)  
 William Hoy Stoner, Bloomfield, N. J. (Lt. Col., MC, AUS)  
 William D. Stubenbord, New York, N. Y. (Comdr., MC, USNR)  
 Harold Sugarman, Saskatoon, Sask., Can. (Capt., R.C.A.M.C.)  
 Frederick Charles Swartz, Lansing, Mich. (Maj., MC, AUS)

Leonard Tarr, New York, N. Y. (Maj., MC, AUS)  
 J. Lawn Thompson, Jr., Washington, D. C. (Capt., MC, AUS)  
 Edward Truman Thorsness, Denver, Colo. (Maj., MC, AUS)  
 Arthur Martin Tiber, New York, N. Y. (Lt. Col., MC, AUS)  
 Pat Alexander Tuckwiller, Charleston, W. Va. (Col., MC, AUS)

David Ulmar, New York, N. Y. (Comdr., MC, USNR)

W. Alfred Van Ormer, Cumberland, Md. (Capt., MC, AUS)  
 Samuel Arthur Vogel, Buffalo, N. Y. (Lt. Col., MC, AUS)

J. Franklin Waddill, Norfolk, Va. (Col., MC, AUS)  
 Otis Sumter Warr, Memphis, Tenn. (Lt. Col., MC, AUS)  
 Bernard Alec Watson, Battle Creek, Mich. (Maj., MC, AUS)  
 George W. Weber, Albany, N. Y. (Maj., USPHS (R))  
 Joseph Francis Whinery, Newark, N. J. (Capt., MC, AUS)  
 Hugh Grigsby Whitehead, Jr., Baltimore, Md. (Comdr., MC, USNR)  
 Alton Floyd Williams, Metter, Ga. (Maj., MC, AUS)  
 Donald Maclean Willson, Rochester, Minn. (Maj., MC, AUS)  
 Sloan Jacob Wilson, Columbus, Ohio (Lt. Col., MC, AUS)  
 William Hoge Wood, Jr., Charlottesville, Va. (Maj., MC, AUS)  
 Andrew Currence Woofter, Parkersburg, W. Va. (Passed Assistant Surgeon,  
 USPHS)

I. Sidney Zaur, Bridgeport, Conn. (1st Lt., MC, AUS)  
 Thomas Ziskin, Minneapolis, Minn. (Maj., MC, AUS)

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#### NEW LIFE MEMBERS OF THE COLLEGE

The College is gratified to announce the following additional Life Members, listed in the order of subscription:

Dr. John Francis Briggs, F.A.C.P., St. Paul, Minn.  
 Dr. Charles Lydon Harrell, F.A.C.P., Norfolk, Va.  
 Dr. Edward James Lynch, F.A.C.P., Shelton, Conn.  
 Dr. George Carlyle Mackie, F.A.C.P., Wake Forest, N. C.  
 Dr. Louis Leo Perkel, F.A.C.P., Jersey City, N. J.  
 Dr. Barnet Packer Stivelman, F.A.C.P., New York, N. Y.  
 Dr. Harold Lindsay Amoss, F.A.C.P., Greenwich, Conn.  
 Dr. Francis Frank Borzell, F.A.C.P., Philadelphia, Pa.  
 Dr. Stanley Erwin, F.A.C.P., Jacksonville, Fla.  
 Dr. William Gilfillan Gardiner, Jr., F.A.C.P., Toledo, Ohio

Dr. Murray Eugene Goodrich, F.A.C.P., Toledo, Ohio  
 Dr. Burton Everett Hamilton, F.A.C.P., Boston, Mass.  
 Dr. Andrew Conway Ivy, F.A.C.P., Chicago, Ill.  
 Dr. Frank Robert Menagh, F.A.C.P., Detroit, Mich.  
 Dr. Harold E. Waxman, F.A.C.P., Pittsburgh, Pa.  
 Dr. Benjamin Franklin Wolverton, F.A.C.P., Cedar Rapids, Iowa  
 Dr. Frank James Montrose, F.A.C.P., Buffalo, N. Y.  
 Dr. Robert Warren Blumenthal, F.A.C.P., Milwaukee, Wis.  
 Dr. Thomas Palmer Sharkey, F.A.C.P., Dayton, Ohio  
 Dr. Henry Johnson Ullmann, F.A.C.P., Santa Barbara, Calif.  
 Dr. Clapham Price King, F.A.C.P., Washington, D. C.  
 Dr. Harry Loren Arnold, Jr., F.A.C.P., Honolulu, T. H.  
 Dr. Joseph Emile Blum, Jr., F.A.C.P., Greenwell Springs, La.  
 Dr. L. Carl Sanders, F.A.C.P., Memphis, Tenn.  
 Dr. Edmond Michael Walsh, F.A.C.P., Omaha, Nebr.  
 Dr. Edward Saunders Dillon, F.A.C.P., Philadelphia, Pa.  
 Dr. Everett Colgate Jessup, F.A.C.P., Roslyn, N. Y.  
 Dr. Frank Louis Williman, F.A.C.P., Washington, D. C.  
 Dr. John Lewis Kleinheksel, F.A.C.P., Wichita, Kan.  
 Dr. Daniel Leritz Sexton, F.A.C.P., St. Louis, Mo.  
 Dr. Henry Hubert Turner, F.A.C.P., Oklahoma City, Okla.  
 Dr. Paul Dudley White, F.A.C.P., Boston, Mass.  
 Dr. Russell S. Boles, F.A.C.P., Philadelphia, Pa.  
 Dr. Douglas Deeds, F.A.C.P., Denver, Colo.  
 Dr. Titus Holliday Harris, F.A.C.P., Galveston, Tex.  
 Dr. Ernest Lynn MacQuiddy, F.A.C.P., Omaha, Nebr.  
 Dr. Treacy Henry Duerfeldt, F.A.C.P., Tacoma, Wash.

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#### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

##### *Books*

"Essentials of Syphilology"—written by R. H. Kampmeier, M.D., F.A.C.P., of the Department of Medicine, Vanderbilt University, Nashville, Tenn.

##### *Reprints*

Hal Davis (Associate), Roanoke, Va.—1 reprint.  
 George Smith Grier, III (Associate), Richmond, Va.—2 reprints.  
 Joseph F. Jenovese, Lt. Comdr., F.A.C.P., San Diego, Calif.—1 reprint.  
 Arthur G. Lueck, Lt. Comdr. (Associate), Washington, D.C.—4 reprints.  
 Joseph T. Roberts (Associate), Washington, D. C.—2 reprints.  
 Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint.  
 Henry L. Smith, F.A.C.P., Detroit, Mich.—1 reprint.  
 Charles LeRoy Steinberg, F.A.C.P., Rochester, N. Y.—1 reprint.  
 Samuel Waldman (Associate), Brooklyn, N. Y.—7 reprints.  
 Charles H. A. Walton, F.A.C.P., Winnipeg, Man., Can.—2 reprints.  
 Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—9 reprints.

## DIRECTORY OF POSTGRADUATE TRAINING OPPORTUNITIES

*Committee on Physical Medicine*

To bring the benefits of Physical Medicine to the rehabilitation of persons maimed in war, industry, or by illness, Bernard M. Baruch in 1944 made an initial grant of \$1,100,000 to establish the Baruch Committee on Physical Medicine, to advance and encourage research, teaching, and training in this special field of medical practice. Eleven medical schools shared funds in the original grants, as follows: Columbia University, New York University, Medical College of Virginia, Massachusetts Institute of Technology, University of Minnesota, University of Southern California, Harvard University, University of Iowa, University of Illinois, Washington University, and Marquette University. The Medical Director of the Baruch Committee on Physical Medicine is Dr. Frank H. Krusen, F.A.C.P., of the Mayo Clinic.

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Saint Louis University School of Medicine offers to physician veterans returning from the Services refresher and advanced professional courses, to be given during the period March 15 to June 8, 1946. Their program consists of five major parts which will encompass approximately 50 Residencies in the St. Mary's Group of Hospitals of St. Louis University, General Refresher and Review courses in Medicine and Surgery for a period of 8 weeks, Refresher and Review Courses in the Specialties for a 4-week period, Specialized Problems in Practice, and Specialized Problems in the Basic Medical Sciences.

No credit for graduate degrees can be obtained through the pursuance of the Refresher and Review Courses. Tuition will be charged at the rate of \$125.00 for an 8-week course and \$62.50 for a 4-week course. Benefits may be obtained under the Servicemen's Readjustment Act (G. I. Bill) by making application on Rehabilitation form 1950, which should be forwarded to the Field Station of the Veterans Administration nearest to the home of the physician veteran. The local office will issue to the veteran a certificate of eligibility and entitlement on Rehabilitation form 1953, which form will be the school's immediate authorization for admitting a student to a course insofar as the financial obligation assumed by the Veterans Administration is concerned. Application for a course should be made on blanks provided by the Registrar of the School of Medicine of Saint Louis University, 1402 South Grand Boulevard, St. Louis 4, Missouri.

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The Department of Public Instruction of the Commonwealth of Pennsylvania has approved the postgraduate courses offered by the American College of Physicians, and has so notified the Pennsylvania State Board of Medical Education and Licensure and the three offices of the Veterans Administration in this District.

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New York University College of Medicine offers postgraduate courses in several branches of medicine to physicians returning from service in the Armed Forces. Civilian physicians are eligible to enroll in these courses. However, medical veterans are given preference in all courses.

The courses come under the provisions of the Servicemen's Readjustment Act of 1944 ("G. I. Bill of Rights") Public Law 346. Any fees in excess of those provided by the Veterans Administration must be paid by the student.

The following types of courses are being offered: (A) Short review ("refresher") courses, part-time and full-time; (B) Longer postgraduate courses, mostly full-time but also available for part-time attendance; and (C) Long-term graduate studies, ranging from 1 to 3 years, practically all of them full-time, and including the basic medical sciences, designed primarily for credit toward certification.

- A. *Short Review Courses*: Arthritis and Rheumatic Disorders; Clinical Gastroenterology; Gastroenterology; Dermatology and Syphilology; Dermatology; Electrocardiography; General Review; Hematology; Internal Medicine; Pediatrics; Radiation Therapy; Syphilis; Urology.
- B. *Longer Postgraduate Courses*: Anesthesia; Cardiovascular Diseases; General Review; Gynecology; Neuropsychiatry; Otorhinolaryngology; Physical Medicine; Proctology; Diagnostic Radiology.
- C. *Graduate Courses*: Anesthesia; Dermatology and Syphilology; Forensic Medicine; Hospital Administration; Ophthalmology; Otorhinolaryngology; Obstetrics and Gynecology; Physical Medicine; Radiation Therapy; Surgery.

#### *Basic Medical Sciences.*

*Fellowships*: A number of fellowships are offered by several of the preclinical and clinical departments of the Medical College. They are usually 1-year appointments and carry a stipend but do not include board or lodging. For further information regarding these fellowships communicate with the Director, Postgraduate Division, New York University College of Medicine, New York 16, N. Y.

#### *Refresher Courses:*

*Recent Advances in Thoracic Surgery*: A full time course of 4 weeks' duration to begin March 4, 1946; minimum number of students, 2; maximum 6. Given under the direction of Dr. Herbert Maier at the Lenox Hill Hospital and Triboro Hospital. Tuition, \$250.00. This course will be repeated in November of 1946.

*Roentgenology*: A postgraduate course on Tuesday and Thursday afternoons between 2:00 and 4:00 o'clock, for two months. It includes review of current films, didactic lectures, and review of museum films. Given at the Beth Israel Hospital under the direction of Dr. Arthur J. Bendick.

*Refresher Course in Psychiatry and Neurology*: Beginning September 17, 1946, an 8 week full-time refresher course in Psychiatry and Neurology will be given for physicians at the New York University College of Medicine, Bellevue Hospital Psychiatric Division, New York City. Only limited enrollment can be accommodated. Tuition fee, \$250.00. Additional information may be obtained from Dr. S. Bernard Wortis, Professor of Psychiatry, New York University College of Medicine, 477 First Avenue, New York 16, N. Y.

*Pathology*: Three part time studies in Pathology of five weeks' duration, given at the Lenox Hill Hospital under the direction of Dr. Rudolf M. Paltauf. Minimum number of students for each group 3, maximum 12.

1. *Gross Pathology for Surgeons, Gynecologists or General Practitioners.* Presentation and discussion of current (fresh) surgical or autopsy specimen. Monday and Thursday evenings from 7 to 8 o'clock.
2. *Histopathology for Surgeons.* Examination of slides from typical inflammatory neoplastic and degenerative surgical lesions. Monday and Thursday evenings from 8 to 9 o'clock.
3. *Histopathology for Gynecologists.* Examination of slides from characteristic lesions of the female genital organs. Tuesday and Friday evenings from 8 to 9 o'clock.

*Internal Medicine*: A part time course of from one to three months' duration, Tuesdays and Thursdays from 2:30 to 4:30 p.m. It consists mainly of bedside teaching, emphasis being placed on the diagnosis and treatment of various medical diseases. Several sessions will be devoted to round table

discussions and lectures on timely subjects. Minimum number of students, 6; maximum, 9. Given at the Beth Israel Hospital under the direction of Dr. Albert A. Epstein.

*Diseases of Metabolism:* A two months' part time course including attendance in three metabolism clinics (Tuesday and Wednesday mornings and Thursday afternoons) and a seminar Tuesday afternoons. Minimum number of students, 2; maximum, 6. Given under the direction of Dr. Elaine P. Ralli.

*Gastroenterology:* A part time course of eight weeks' duration, Mondays from 3:00 to 5:00 p.m. and Fridays from 10:00 to 12:00 a.m. Minimum number of students, 6; maximum, 10. Given at the Beth Israel Hospital under the direction of Dr. Michael Weingarten.

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A two weeks' refresher course in General Medicine will be held during the month of March at Richmond, Virginia, under the auspices of the Medical College of Virginia, and repeated again in September, 1946. In Charlottesville, Virginia, a similar refresher course has been arranged for returning veteran medical officers during the month of June. These courses consist of 36 lectures, 20 clinics, and 40 ward rounds. In addition, 10 evening sessions will be presented during the fortnight. The charge for each course is \$40 and the attendance is limited to 50 registrants.

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The Medical Faculty of the University of Michigan is offering a Postwar Program of Training and Review Courses for returning medical officers and civilian physicians.

Among the courses offered is a two-month course in Internal Medicine, being given March 4 through April 27, 1946, consisting of daily ward rounds, lectures, seminars, and conferences. All subjects in internal medicine are discussed with emphasis on clinical problems and the therapeutic approach.

Immediately following, a Course for Practitioners will be given April 29 through June 22. Clinics, lectures, demonstrations, and ward rounds will be used to present the following subject material: Minor surgery in office practice; non-operative gynecology and obstetrics; otolaryngology and ophthalmology; treatment of venereal diseases, dermatological lesions, burns; general medical practice; infectious diseases, pediatric practice; neurology and psychiatry.

In connection with the above courses, daily lecture demonstrations in Pathology will be given throughout the period.

Brief, review courses of three to five days also will be given during May and June, as follows: Allergy, Diseases of the Heart, Diseases of the Blood, Endocrinology and Metabolism, Recent Advances in Therapeutics, and Gastroenterology.

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A Postgraduate Course in Diseases of the Chest will be given under the auspices of the Illinois Chapter of the American College of Chest Physicians at Michael Reese Hospital, Chicago, Illinois, during the week April 1 to 6, inclusive.

Doctors may elect to follow this week's formal course with practical instruction in the fields of thoracic surgery, bronchoscopy, pneumothorax, bronchography, and other methods and technics in the diagnosis and treatment of pulmonary disease.

Further information may be secured at the office of the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

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#### SPRING POSTGRADUATE COURSES

An index of ten postgraduate courses sponsored by the American College of Physicians, to be given by various Directors this spring, is listed below.

The course in Clinical Allergy has been divided into three sections, limited to 6 registrants each. Sections A and B are now filled, but application can be made for Section C to be given from July 8 to July 13, 1946.

The course in General Medicine to be given at the Jefferson Medical College presents an excellent program dealing with practical demonstration of problems in Internal Medicine.

The course in General Medicine at the University of Texas School of Medicine, Galveston, promises to be well worthwhile, and should be of particular interest to members of the College living in the South and West.

Course No. 4 in Internal Medicine, at the Massachusetts General Hospital, has now been oversubscribed and no further applications can be received for this course.

An intensive personalized course in Nutrition will be conducted by Dr. Tom D. Spies at the Nutrition Clinic of the Hillman Hospital in Birmingham, Alabama, from June 3 to June 8, inclusive. Dr. Spies will conduct this course and present among other important data a summary of his recent observations on the problem of Nutritional Anemias in Cuba.

The faculty of Emory University Medical School in Atlanta, Georgia, has organized a splendid program in General Medicine to be given from April 22 to April 27.

The course in Gastro-enterology, from April 29 to May 4, and the course in Cardiology from May 6 to May 11, both of which will be given in Philadelphia, are rapidly filling up.

An excellent symposium on Thoracic Diseases has been organized by the faculty of the University of Michigan Medical School and Hospital, to be given at Ann Arbor from May 6 to May 11.

The dates for Course No. 10, Internal Medicine, at the University of California Medical School and Medical Center, in San Francisco, have been moved up to June 17-June 28, inclusive, immediately preceding the Convention of the American Medical Association from July 1 to July 5, 1946.

The fees for Course 1, in Allergy, and for Course 5, in Nutrition, will be \$40.00 per week to members and \$80.00 per week to non-members.

The fee for Course No. 10 in Internal Medicine at the University of California, which is of 2 weeks' duration, will be \$40.00 to members and \$80.00 to non-members.

A copy of the Final Bulletin of Spring Courses has been mailed to all members of the College and to interested non-members whose addresses are on file at the College Headquarters.

#### INDEX

- Course No. 1—Clinical Allergy
  - Massachusetts General Hospital
  - Boston, Massachusetts
  - Section A—March 4-9, 1946
  - Section B—April 8-13, 1946
  - Section C—July 8-13, 1946
- Course No. 2—General Medicine
  - Jefferson Medical College
  - Philadelphia, Pa.
  - (1 week—March 18-23, 1946)
- Course No. 3—General Medicine
  - University of Texas School of Medicine
  - Galveston, Texas
  - (1 week—March 25-30, 1946)



- Course No. 4—Internal Medicine  
Massachusetts General Hospital  
Boston, Massachusetts  
(3 weeks—April 1-18, 1946)
- Course No. 5—Nutrition  
Nutrition Clinic, Hillman Hospital  
Birmingham, Alabama  
(1 week—June 3-8, 1946)
- Course No. 6—General Medicine  
Emory University  
School of Medicine  
Atlanta, Georgia  
(1 week—April 22-27, 1946)
- Course No. 7—Gastro-enterology  
Graduate Hospital  
Philadelphia, Pa.  
(1 week—April 29-May 4, 1946)
- Course No. 8—Cardiology  
Philadelphia General Hospital and  
Woman's Medical College of Pennsylvania  
Philadelphia, Pa.  
(1 week—May 6-11, 1946)
- Course No. 9—Chest Diseases  
University of Michigan  
Medical School and Hospital  
Ann Arbor, Michigan  
(1 week—May 6-11, 1946)
- Course No. 10—Internal Medicine  
University of California Medical School and  
Medical Center  
San Francisco, California  
(2 weeks—June 17-28, 1946)

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Captain Hugh Tatlock, (MC), AUS, of Weston, Massachusetts, has been awarded a Clinical Fellowship in Medicine sponsored by the American College of Physicians, for one year, to work under Dr. Francis G. Blake and Dr. J. J. Peters, in the Department of Internal Medicine, Yale School of Medicine, New Haven, Conn.

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Dr. George F. Lull, F.A.C.P., formerly deputy Surgeon General, United States Army Medical Corps, has been appointed Associate General Manager of the American Medical Association, as of January 1, 1946.

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Dr. Henry L. Smith, F.A.C.P., Chief of Staff of the Mount Carmel Mercy Hospital, Detroit, and Dr. P. L. Ledwidge, F.A.C.P., who is Speaker of the House of Delegates of the Michigan State Medical Society, addressed the staff and their guests at the Annual Clinic Day of the Mount Carmel Mercy Hospital on January 30, 1946.

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Dr. Robert Collier Page, F.A.C.P., a medical officer in the Army Air Forces during World War II and Assistant Medical Director of the Standard Oil Company

(New Jersey) has been appointed General Medical Director of the Company, succeeding Dr. Willard J. Denno, F.A.C.P., who will continue with the Company as Medical Consultant.

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OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the Army, addressed a meeting held in Washington on January 10, 1946, opening the program to erect a Nurses National Memorial with a minimum \$2,000,000 goal.

Colonel James E. Ash, F.A.C.P., Director of the Army Medical Museum, has been awarded the Legion of Merit for his efficiency in organizing the most extensive tissue pathology service ever known to the world.

Brigadier General William C. Menninger, F.A.C.P., Director of the Neuropsychiatry Consultants Division of The Surgeon General's Office, is sponsoring an orientation program for Armed Forces in the Pacific areas, implemented by the United States Armed Forces Institute which provides soldiers with University opportunities while on occupation duty.

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Vice Admiral Ross T. McIntire, MC, USN, F.A.C.P., Chief of the Bureau of Medicine and Surgery and The Surgeon General of the Navy, recently received the Distinguished Service Medal for his outstanding achievements during the war and especially "for exceptionally meritorious service to the Government of the United States." Other decorations held by Admiral McIntire include those from the following foreign countries: Brazil, Sweden, Belgium, France, Luxembourg, Denmark, Poland, Nicaragua, Norway and French Morocco.

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Colonel Charles C. Gill (Associate), MC, U. S. Army, whose home address is Balboa, California, but who is at present commanding the 193rd General Hospital, has received the Bronze Star of the United States and the Medal of Merit, 1st class, from the Czechoslovakian Government, in recognition of outstanding work during the war.

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Dr. Elmer L. Sevringhaus, F.A.C.P., A.C.P. Governor for Wisconsin for many years, has resigned his position as Professor of Medicine at the University of Wisconsin Medical School, and Physician, State of Wisconsin General Hospital, and on March 1, 1946, became Director of Clinical Research for Hoffman-LaRoche, Incorporated, Nutley, N. J. He is residing at 59 Warren Place, Montclair, N. J.

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Dr. Charles T. Chamberlain, F.A.C.P., Fort Smith, Arkansas, recently addressed the Ninth Councilor District Medical Society at Harrison on "Heart and Aviation."

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Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., has been appointed Deputy Medical Director of the State Department of Mental Hygiene in California.

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Dr. Edward H. Hashinger, F.A.C.P., Professor of Clinical Medicine at the University of Kansas School of Medicine, is Acting Director of the Division of Graduate Medical Education of the University of Kansas School of Medicine.

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The following Fellows of the College addressed the Third Annual Medical and Surgical Symposium of the Watts Hospital, Durham, North Carolina, on February 13, 1946: Dr. Wilburt C. Davison, Durham; Dr. Edward A. Strecker, Philadelphia; Dr. James E. Paullin, Atlanta; Dr. Louis Hamman, Baltimore; and Dr. Eugene P. Pendergrass, Philadelphia.

Dr. Abe Ravin, F.A.C.P., Denver, Colo., Dr. Ferdinand R. Schemm, F.A.C.P., of Great Falls, Mont., Dr. Maxwell M. Wintrobe, F.A.C.P., of Salt Lake City, Utah, and Dr. Irving S. Wright, F.A.C.P., of New York City, were among the speakers to address the first Regional Meeting of the Western Section of the American Federation for Clinical Research, held under the auspices of the University of Utah School of Medicine, Salt Lake City, at the Salt Lake County General Hospital.

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Dr. A. V. Molyneux, F.A.C.P., Honolulu, T. H., visited the College Headquarters on January 24, 1946.

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Dr. Roy E. Butler, F.A.C.P., Senior Surgeon, USPHS, has been detailed by the National Institute of Health, Division of Physiology, to the Tulane University School of Medicine to cooperate in certain nutritional investigations to be carried on there.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health, City and County of San Francisco, has been awarded the "Ordre de la Santa Publique" by the Government of the French Republic in recognition of the distinguished service rendered France as Director of Public Health in San Francisco.

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Brigadier General James S. Simmons, U. S. Army, F.A.C.P., Chief of the Preventive Medicine Service of the Office of The Surgeon General, and President of the American Society of Tropical Medicine, has been appointed Dean of the Harvard University School of Public Health, to begin his duties on July 1, 1946. The Rockefeller Foundation has granted \$1,000,000 for expenses of the School of Public Health for a 10-year period from July 1946 to July 1956, and Harvard University has set aside an additional sum of \$750,000 as an endowment for the school to supplement the present endowment fund during the coming decade. The school has recently acquired the Collis P. Huntington Memorial Hospital to carry on its pioneer work in Industrial Hygiene and Child Health.

Dr. Edward Huber, F.A.C.P., is Acting Dean of the Harvard University School of Public Health.

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Dr. Warfield T. Longcope, F.A.C.P., Professor of Medicine at Johns Hopkins University School of Medicine, Baltimore, will retire June 30, 1946, ending twenty-four years of distinguished service to the Medical School and the Johns Hopkins Hospital.

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Dr. Tinsley R. Harrison, F.A.C.P., Professor of Internal Medicine and Chairman of the Department of Medicine and Dean of the Southwestern Medical College, Dallas, Texas, recently received the Research Medal of the Southern Medical Association "in recognition of his outstanding contributions toward the elucidation of structural and functional aspects of cardiovascular disease and particularly of practical problems arising from failure of the circulation."

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Lt. Col. Arthur M. Tiber, F.A.C.P., Baltimore, received from the Government of the Republic of China the Army, Navy and Air Forces Decoration, 1st Class, in recognition of his sincere and distinguished services with the Chinese Chronic Hospital of the Chinese Army in India.

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Dr. Philip Goldstein (Associate), New York City, was awarded the Bronze Star for services with the Army in Italy.

Dr. Alfred Gordon, F.A.C.P. and Dr. Daniel J. McCarthy, F.A.C.P., members of the Philadelphia County Medical Society, have completed fifty years in the practice of medicine and received framed certificates to this effect from the Medical Society of the State of Pennsylvania.

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Dr. Clarence A. Smith, F.A.C.P., Seattle, Wash., has completed forty-two years of service as Editor of *Northwest Medicine*.

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Dr. George Smith Grier, III (Associate), formerly of Newport News, Va., is now retired from active service in the Army and is pursuing a fellowship in Pathology at the Medical College of Virginia, Richmond.

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Dr. Ward Darley, F.A.C.P., College Governor for Colorado, is now the permanent Dean of the University of Colorado School of Medicine.

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Dr. Paul K. French, F.A.C.P., has retired from active duty in the Army and resumed the practice of Internal Medicine in Burlington, Vermont. Dr. French also resumed his post as the College Governor for Vermont. Dr. Ellsworth L. Amidon, F.A.C.P., of Burlington, served as Acting Governor during Dr. French's absence in the Army from 1942 to the latter part of 1945.

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Dr. Carl J. W. Wilen, F.A.C.P., has recently retired from the Army and is now the Internist at the Nelson Clinic, Manhattan, Kansas.

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Dr. George Newton Barry, F.A.C.P., Oklahoma City, is serving on active duty in the Medical Corps of the U. S. Naval Reserve. His entry upon active duty has not previously been announced.

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The total number of members of the College recorded on active duty during World War II was 1,929.

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According to *Science News Letter* for February 2, 1946, members of the Medical Corps of all Services, officers and enlisted men alike, won 6 per cent of all decorations for service beyond the call of duty.

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Dr. James A. Mansmann (Associate), is the new President of the Pittsburgh Allergy Society.

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Dr. Francis F. Borzell, F.A.C.P., Philadelphia, was recently chosen Vice President of the American Roentgen Ray Society.

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Dr. Roy W. Scott, F.A.C.P., Cleveland, was named President; Dr. Carl V. Moore, F.A.C.P., St. Louis, Vice President; and Dr. Ford K. Hick, F.A.C.P., Chicago, Secretary-Treasurer of the Central Society for Clinical Research.

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Dr. James S. Simmons, F.A.C.P., Washington, D. C., was recently elected President of the American Academy of Tropical Medicine, and Dr. Thomas T. Mackie, F.A.C.P., New York, Treasurer.

Dr. Clarence E. Reyner, F.A.C.P., Henry Ford Hospital, Detroit, is Secretary of the Central States Dermatological Society.

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Dr. Joseph D'Antoni, F.A.C.P., New Orleans, was recently elected Vice President of the American Society of Tropical Medicine.

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Dr. Arthur S. Webb, F.A.C.P., Wheaton, Ill., has been elected Vice President of the Chicago Tuberculosis Society.

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Dr. Andrew D. Hart, F.A.C.P. (Lt. Col., MC, AUS, retired), was recently elected Veterans Representative of the Medical Society of Virginia.

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Dr. Staige D. Blackford, F.A.C.P., has been placed in charge of the Postwar Program for returning medical veterans at the University of Virginia and Dr. James P. Baker, F.A.C.P., is in charge of a similar program at the Medical College of Virginia, Richmond.

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Dr. R. Finley Gayle, Jr., F.A.C.P., of Richmond, is Chairman of the Virginia State Hospital Board. He states that there is a need for five Clinical Directors at salary rates of about \$5,000 annually, and several Assistant Physicians, to serve in the Psychiatric Department of the Virginia State Hospital System.

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The Hermann M. Biggs Memorial Lecture, which is delivered annually in Hosack Hall at the New York Academy of Medicine under the auspices of the Committee on Public Health Relations, will be delivered this year on Thursday, April 4, at 8:30 p.m. by Laurence H. Snyder, Sc.D., Professor of Medical Genetics, Department of Medicine, Ohio State University. The subject of the lecture will be "Medical Genetics and Public Health."

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Dr. Joseph T. Roberts (Associate), of Washington, D. C., has recently participated in the following scientific meetings at which he presented articles, as indicated: Society for Experimental Biology and Medicine, District of Columbia Section, "Significance of the Blood Supply of Peripheral Nerves"; American Federation for Clinical Research, Eastern Section Meeting, "The Clinical Use of Globin Zinc Insulin, Protamine Zinc Insulin, and Mixed Insulin"; and Washington Heart Association, "Infarction of the Right Ventricle and Thrombosis of a Congenital Single Coronary Artery—Review of Cases at Gallinger Municipal Hospital and Army Medical Museum," with Dr. Samuel D. Loube, and "Current Concepts of Digitalis-Like Drugs."

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Dr. Max Pinner, F.A.C.P., New York City, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, delivered the second Dr. Reginald Knight Smith Lecture on January 24, 1946, at the Mount Zion Hospital, San Francisco. He discussed "Modern Trends in the Treatment of Pulmonary Tuberculosis."

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The annual Tufts Medical Alumni Lecture was given on February 20, 1946, at the Tufts College Medical School, Boston, by Dr. Winthrop Adams, F.A.C.P., who is Manager of the Veterans Administration Facility at Bedford, Mass. Dr. Adams was recently appointed Deputy Surgeon General of one of the thirteen United States districts formed under the reorganization plan of the Veterans Administration.

Dr. Anton J. Carlson, F.A.C.P., Emeritus Professor of Physiology, University of Chicago School of Medicine, recently delivered the 94th annual commencement address, entitled "The Endless Frontiers in Medicine," before the graduating class of the Woman's Medical College of Pennsylvania, Philadelphia.

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Dr. Bruce K. Wiseman, F.A.C.P., Columbus, Ohio, presented a paper entitled "Hypersplenism and the Blood Dyscrasias" before the 11th annual midwinter Post-graduate Clinics conducted by the Colorado State Medical Society.

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Dr. J. Owsley Manier, F.A.C.P., Nashville, Tenn., served as toastmaster at the combined dinner of the Nashville Academy of Medicine and the Davidson County Medical Society in honor of Dr. Harrison H. Shoulders, Nashville, President-elect of the American Medical Association. Among the speakers introduced by Dr. Manier were: Dr. William C. Chaney, F.A.C.P., Memphis; Dr. Ernest R. Zemp, F.A.C.P., Knoxville; and Dr. Ernest E. Irons, F.A.C.P., Chicago.

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Dr. William Dameshek, F.A.C.P., Boston, Mass., recently delivered a series of lectures at the Medical School of the National University of Mexico, in which he discussed the "Physiologic Principles in Anemia," "Disorders of the Spleen," and "Hemolytic Syndromes."

The title of Professor of Medicine, Extraordinary, was conferred upon Dr. Dameshek at the conclusion of this series.

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Dr. R. K. Richards, F.A.C.P., North Chicago, Ill., recently addressed a group at the University of Utah at Salt Lake City on "Inhibition of Central Convulsions Caused by Procaine by Its Split Products."

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Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, Consultant in Chemotherapy to the National Research Council, was a guest speaker at the first Refresher Course for Veterans sponsored by the Department of Medicine of the University of Virginia in Charlottesville.

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Dr. Harold G. Wolff, F.A.C.P., New York City, will direct a project in Internal Medicine at the New York Hospital, dealing with Psychosomatics, as authorized by Cornell University. This project provides for six Fellowships, Fellows to be appointed for a period of one year with the expectation of serving for two or more. The Fellowship awards for the first year provide a salary of \$2,500 each. Prospective candidates should arrange for a personal interview through Dr. David P. Barr, F.A.C.P., President-elect of the American College of Physicians, at the New York Hospital, 525 East 68th Street, New York.

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The next Annual Meeting of the American College of Radiology is tentatively scheduled to be held in San Francisco on June 29, 1946.

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The 28th Annual Meeting of the American Dietetic Association will be held at the Netherland Plaza, Cincinnati, Ohio, October 14 through 18, 1946.

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The 1946 Assembly of the Interstate Postgraduate Medical Association of North America will be held at the Public Auditorium in Cleveland, Ohio, Tuesday to Friday, inclusive, October 15-18, 1946.

The annual meeting of the American Society for Research in Psychosomatic Problems, of 714 Madison Avenue, New York City, will be held at the Hotel Pennsylvania, New York, on May 11 and 12, 1946. Listed on the program for May 11 are the following subjects: "Contributions of Military Medicine to Psychosomatic Medicine"; "Psychosomatic Aspects of Orthopedic Practice"; and "New Advances in Psychosomatic Investigative Techniques."

Because of space limitation, reservations should be made at least two weeks prior to meeting. Registration fee for non-members is \$5.00 for two days; \$3.00 for one. The charge for the Annual Dinner is \$5.00. Limited hotel reservations are available.

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The A.P.A.A. (Ninth) 1947 Exhibition to be held at Atlantic City, on the occasion of the Centennial Session of the American Medical Association, will also be the occasion of the judging of the "Courage and Devotion Beyond the Call of Duty" Art Prize Contest (\$34,000 in Savings Bonds).

This contest was originally scheduled for the 1946 A.M.A. Session but has been postponed one year, upon the best advice, in order to give more physicians an additional year to complete their art pieces on this special prize subject.

For further information regarding both the San Francisco 1946 and the Atlantic City 1947 Art Exhibits, physicians may write either the American Physicians Art Association, Secretary-Treasurer, Dr. Francis H. Rodowill, Flood Building, San Francisco, Calif., or the sponsor, Mead Johnson & Co., Evansville, Ind.

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Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., and Dr. W. O. Thompson, F.A.C.P., are members of the Executive Committee of the Mississippi Valley Medical Society, whose next meeting will be held at the Hotel Jefferson, St. Louis, September 25, 26, and 27, 1946.

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The annual meeting of the American Association for the Study of Goiter will be held at the Drake Hotel, Chicago, Illinois, on June 20, 21, and 22.

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The New York University College of Medicine is sponsoring an extensive program of departmental reorganization and \$15,000,000 expansion of their physical plant to meet the present problems of modern medicine. Bellevue Hospital is to be largely rebuilt by the City of New York at a cost of \$12,500,000. This project, totaling \$27,500,000, is being shaped to meet medicine's new perspectives and provides an unsurpassed opportunity to develop these two institutions. Dr. Currier McEwen, F.A.C.P., is Dean of the New York University College of Medicine, and Dr. Clarence E. de la Chapelle, F.A.C.P., is Assistant Dean in Charge of Postgraduate and Graduate Education. Dr. Samuel A. Brown, F.A.C.P., is a member of the University Council of New York University, and Dr. S. Bernard Wortis, F.A.C.P., is a member of the Faculty Executive Committee.

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### SPECIAL NOTICES

*Urology Award*—The American Urological Association offers an annual award "not to exceed \$500" for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Netherland Plaza, Cincinnati, Ohio, July 22-25, 1946.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before July 1, 1946.

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Appointments to fill vacancies in the Reserve Corps of the United States Public Health Service are now being made, and examinations for Regular Corps appointments will be held in April and May, Surgeon General Thomas Parran announced.

Physicians, dentists, and nurses are needed immediately for duty in hospitals, in the Tuberculosis and Venereal Disease Control programs, and in other activities of the Public Health Service.

Pay and allowances, established by law, are identical with those for medical officers of the Army. All travel expenses, including travel to first station, are paid by the Service.

Appointments to the Reserve Corps are made on a basis of review of data furnished by the applicant. Physical examination is required.

Regular Corps appointments require appearance before a Board, and a written professional examination. Dates and places for the examination will be announced shortly.

The Service pointed out that a person receiving an appointment in the Reserve Corps immediately, may, if he desires, take the examination for the Regular Corps at the time they are held.

Those interested in either immediate appointment in the Reserve Corps, or in taking the examination for the Regular Corps, should request application forms of the Surgeon General, U. S. Public Health Service, Washington, D. C., Federal Security Agency.

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Cornell announces a project in internal medicine at the New York Hospital, designed to deal clinically and experimentally with psychosomatics. There are three main objectives: (1) To develop a practical method of dealing with ambulatory clinic patients who suffer from symptoms related to their emotional states and life situations. (2) To engage in experimental study of the mechanisms involved in illness of this nature, and (3) to train especially able young physicians in experimental methods and a critical psychosomatic approach to the care of the sick. Approximately half time will be spent in the diagnosis and management of patients and half time in research dealing mainly with mechanisms underlying symptoms.

The project will be directed by Dr. Harold G. Wolff with the assistance of an internist, Dr. Stewart Wolf; a psychiatrist, Dr. Herbert S. Ripley, Jr. and six fellows. Fellows will be appointed for a period of one year with the expectation of serving for two or more. Their salary for the first year will be \$2500. Candidates for fellowship should have at least two years training in internal medicine and have given evidence of a psychiatric orientation. They need not necessarily have had experience in research but must have a serious interest in investigation, energy and curiosity.

Prospective candidates should arrange for a personal interview through Dr. David P. Barr, Professor of Medicine, The New York Hospital, 525 East 68 Street, New York City, N. Y.



## PROGRAM

(Tentative; Subject to Change)

### TWENTY-SEVENTH ANNUAL SESSION PHILADELPHIA, PA.

May 13-17, 1946

#### GENERAL SESSIONS AND LECTURES

Ernest E. Irons, President

#### PHILADELPHIA COMMITTEE ON ARRANGEMENTS

George Morris Piersol, Chairman

Edward L. Bortz

Harrison F. Flippin

Thomas Fitz-Hugh, Jr.

Richard A. Kern

Francis Wood

#### COMMITTEE ON CLINICS

Thomas Fitz-Hugh, Jr., Chairman

Joseph Stokes

Children's Hospital

Henry L. Bockus

Graduate Hospital of the University of Pennsylvania

G. Harlan Wells

Hahnemann Medical College and Hospital

T. Grier Miller

Hospital of the University of Pennsylvania

Kenneth E. Appel

Institute of the Pennsylvania Hospital

Hobart A. Reimann

Jefferson Hospital

Joseph C. Doane

Jewish Hospital

Edward L. Bortz

Lankenau Hospital

David Cooper

Pennsylvania Hospital

Truman G. Schnabel

Philadelphia General Hospital

Joseph T. Beardwood, Jr.

Presbyterian Hospital

Charles L. Brown

Temple University Medical School and Hospital

Walter H. Schwartz

U. S. Naval Hospital

William G. Leaman, Jr.

Woman's Medical College

#### COMMITTEE ON HOTELS AND TRANSPORTATION

Harrison F. Flippin, Chairman

Charles W. Dunn

Daniel B. Pierson

Ferdinand Fetter

Rufus S. Reeves

#### COMMITTEE ON ENTERTAINMENT

Edward L. Bortz, Chairman

Thomas M. Durant

D. Sergeant Pepper

Merle M. Miller

William Harvey Perkins

**COMMITTEE ON PUBLICITY**

Richard A. Kern, Chairman

Garfield G. Duncan  
Thomas M. DurantSimon S. Leopold  
John H. Willard**COMMITTEE ON PANEL DISCUSSIONS**

Francis C. Wood, Chairman

W. Wallace Dyer  
Kendall A. ElsomHarrison F. Flippin  
Edward Rose

Charles C. Wolferth

**COMMITTEE ON TECHNICAL EXHIBITS**

George Morris Piersol, Chairman

Thomas Klein

Charles C. Wolferth

**COMMITTEE ON LADIES' ENTERTAINMENT**

Mrs. William D. Stroud, Chairman

Mrs. Russell S. Boles  
Mrs. Edward L. Bortz  
Mrs. Francis F. Borzell  
Mrs. Charles L. Brown  
Mrs. Robin C. Buerki  
Mrs. W. Edward Chamberlain  
Mrs. David A. Cooper  
Mrs. Thomas M. Durant  
Mrs. Kendall A. Elsom  
Mrs. Thomas Fitz-Hugh, Jr.  
Mrs. Harrison F. Flippin  
Mrs. J. Warren HundleyMrs. Harold W. Jones  
Mrs. Richard A. Kern  
Mrs. Thomas M. McMillan  
Mrs. Hugh Montgomery  
Mrs. O. H. Perry Pepper  
Mrs. Wm. Harvey Perkins  
Mrs. George Morris Piersol  
Mrs. Truman G. Schnabel  
Mrs. Joseph B. Vander Veer  
Mrs. G. Harlan Wells  
Mrs. Charles C. Wolferth  
Mrs. Francis C. Wood**HONORARY COMMITTEE**

Living Past Presidents

James E. Paullin  
Roger I. Lee  
James D. Bruce  
O. H. Perry Pepper  
William J. Kerr  
James H. Means  
Ernest B. BradleyJames Alex. Miller  
Jonathan C. Meakins  
George Morris Piersol  
Francis M. Pottenger, Sr.  
S. Marx White  
Sydney R. Miller  
John H. Musser

Charles F. Martin

**INVITATION**

Philadelphia, cradle of American medicine and "cradle of liberty," its medical profession and medical institutions extend to members of the American College of Physicians a most cordial welcome to this city for the Twenty-Seventh Annual Session. The College of Physicians of Philadelphia, the Philadelphia County Medical Society, the deans of the various medical schools—the University of Pennsylvania School of Medicine and Graduate School of Medicine, the Jefferson Medical College

of Philadelphia, the Woman's Medical College of Pennsylvania, the Hahnemann Medical College and Hospital, the Temple University School of Medicine—the Department of Public Health, the United States Naval Hospital, and a group of hospitals centrally located have coöperated with the local Fellows of the College in preparing a program which should prove instructive, interesting, and stimulating to all. Many distinguished physicians from various parts of the United States and Canada will contribute to the program.

Exceptional interest should be attached to this meeting not only because it is the first occasion since 1935 that Philadelphia has had the opportunity to be host to the College, but also because this is the first meeting of the College as a whole since the outbreak of World War II. This occasion may well be called the "Victory Session," marking the return of American medicine to normal peacetime activities. During the years that have elapsed since the last Philadelphia meeting our medical institutions, despite the handicaps imposed by war resulting in depleted personnel and preoccupation in efforts to solve the urgent problems presented by our armed forces, have continued to expand and develop, particularly in research and teaching facilities. In addition to the attendance at clinics, ward rounds, panel discussions, laboratory demonstrations and lectures, members of the College are invited to inspect, at their greater leisure, these Philadelphia medical institutions.

Philadelphia offers other attractions than those purely medical. Mention may be made of Independence Hall and the Liberty Bell, Congress Hall, Betsy Ross House, Christ Church, Old Swedes, Pennsylvania Academy of Fine Arts, the Academy of Natural Sciences, Public Library, Art Museum, Rodin Museum, University Museum, Franklin's Grave, the Zoölogical Gardens, Fairmount Park wherein may be found William Penn's House, Memorial and Horticultural Halls, the Aquarium, Washington Monument, Philadelphia Navy Yard, United States Mint and the Franklin Institute with its Planetarium.

It is the earnest hope of those who have prepared this program that this "Victory Session" may indeed prove one of the most memorable of the long series of important meetings of the College and that the stay of every guest will be enjoyable and profitable.

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## GENERAL INFORMATION

### GENERAL HEADQUARTERS

Convention Hall

34th Street below Spruce

Registration headquarters, information bureau, technical exhibits, general sessions, morning lectures and panel discussions.

### HOTEL HEADQUARTERS

Benjamin Franklin Hotel

9th & Chestnut Sts.

The Benjamin Franklin Hotel will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the Benjamin Franklin Hotel cannot fill will be referred immediately to some other hotel on the following list.

Hotels	Approx. City Blocks from Convention Hall	Available Rooms	Rates
BENJAMIN FRANKLIN Edmund Flynn, Sales Mgr. 9th & Chestnut Sts.	28	50 Single 325 Double 25 Suites	\$3.50 up 5.50 up
Adelphia Kenneth W. Baker, Mgr. 13th & Chestnut Sts.	24	50 Double	5.00 up
Barclay Arthur T. Murray, Mgr. 18th & Locust Sts.	18	10 Double 3 Suites	7.00 up
Bellevue-Stratford Floyd E. Rush, Mgr. Broad & Walnut Sts.	22	75 Double	6.00 up
Chateau Crillon James T. Quinlan, Mgr. 1900 Locust St.	17	5 Double	6.00 up
Drake Wm. F. Hamilton, Mgr. 1512 Spruce St.	20	25 Double	5.50 up
Essex Percy W. Shelley, Res. Mgr. 13th & Filbert Sts.	25	15 Single 30 Double	3.00 up 4.50 up
Lorraine D. Dewey Davis, Mgr. Broad St. & Ridge Ave.	33	10 Double	5.00
Majestic Charles H. Pelot, Mgr. Broad St. & Girard Ave.	37	30 Double 3 Suites	4.00 up 10.00
Normandie Lloyd R. Woods, Mgr. 36th & Chestnut Sts.	4	30 Double	4.00 up
Parker John J. Guthrie, Mgr. 13th & Spruce Sts.	22	20 Single 15 Double	2.50 up 3.50 up
Philadelphian Daniel Crawford, Jr., Mgr. 39th & Chestnut Sts.	7	175 Double	4.50 up
Ritz-Carlton J. Martin Hardy, Mgr. Broad & Walnut Sts.	22	15 Double	6.50 up
Robert Morris Louis E. Pike, Mgr. 17th & Arch Sts.	22	15 Single 25 Double	2.50 up 4.00 up
St. James William H. Harned, Mgr. 13th & Walnut Sts.	23	5 Single 35 Double	2.75 4.50 up
Sheraton Kurt A. Smith, Mgr. 19th & Walnut Sts.	17	10 Double 8 Suites	6.50 up 8.50
Sylvania Reginald G. Nefzger, Mgr. Juniper & Locust Sts.	22	30 Double	5.00 up
Walton C. Pitman Baker, Jr., Mgr. Broad & Locust Sts.	22	10 Single 65 Double	2.50 up 4.00 up
Warwick Joseph Hoenig, Mgr. 17th & Locust Sts.	19	10 Single 40 Double	5.00 up 8.00 up

Hotel facilities are limited; members are urged to use double rooms, sharing with other physician friends, due to the shortage of single rooms.

Apply directly for reservations to the hotel of your choice. Physicians should mention specifically the fact that reservations are being made in connection with the Annual Session of The American College of Physicians.

## DIRECTORY

General Headquarters.....	Convention Hall, 34th St. below Spruce
Hotel Headquarters.....	Benjamin Franklin Hotel, 9th & Chestnut Sts.
General Registration.....	Exhibition Floor, Convention Hall
Board of Regents.....	Room 101, Exhibition Floor, Convention Hall
Board of Governors.....	Room 101, Exhibition Floor, Convention Hall
Executive Secretary's Office.....	Room 103, Exhibition Floor, Convention Hall
Press Room.....	Room 205, Arena Floor, Convention Hall
Technical Exhibits.....	Exhibition Floor, Convention Hall
General Scientific Sessions.....	Arena, Convention Hall
Morning Lectures.....	Ballroom, Convention Hall
Panel Discussions.....	Various Rooms, Convention Hall
Musical Concert, Orpheus Club.....	Ballroom, Benjamin Franklin Hotel
Convocation.....	Ballroom, Benjamin Franklin Hotel
Annual Banquet.....	Ballroom, Benjamin Franklin Hotel
Ladies' Registration and Headquarters...	Mezzanine Floor, Benjamin Franklin Hotel

## WHO MAY REGISTER—

- (a) All members of The American College of Physicians in good standing for 1946 (dues, if not paid previously, may be paid at the Registration Bureau).
- (b) All newly elected members.
- (c) Senior medical students pursuing courses at the University of Pennsylvania, Jefferson Medical College, Hahnemann Medical College, Temple University and Woman's Medical College, without registration fee, upon presentation of matriculation cards or other evidence of registration at these institutions; exhibits, general sessions and morning lectures only.
- (d) Members of the staff, including internes, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, general sessions and morning lectures.
- (e) Members of the College of Physicians of Philadelphia and of the Philadelphia County Medical Society, without registration fee, upon presentation of 1946 membership cards; exhibits, general sessions and morning lectures.
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (g) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

**Registration Bureau**—Temporary Registration Bureau will be open at the Convention Hall on Sunday, May 12, from 2:30 to 5:00 in the afternoon. The per-

manent Registration Bureau at the Convention Hall will be open daily 8:30 A.M. to 5:45 P.M., Monday to Friday, May 13-17.

**Registration Blanks for All Clinics and Panel Discussions** are sent with the program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

**Bulletin Boards** for special announcements will be located near the Registration Bureau at Convention Hall and in the lobby of the headquarters hotel.

**Transportation**—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

**The General Business Meeting** of the College will be held at 4:30 P.M., Thursday, May 16, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

\*There will be the election of Officers, Regents and Governors and the annual reports of the Secretary General, Executive Secretary and Treasurer will be presented. The President-Elect, Dr. David P. Barr, New York, N. Y., will be inducted into office.

**Board and Committee Meetings**—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A dinner meeting of the Board of Regents and of the Board of Governors will be held at the Benjamin Franklin Hotel, mezzanine floor, Sunday evening, May 12, at 7 o'clock.

#### COMMITTEE ON CREDENTIALS

Sunday, May 12, 9:15 A.M.....Convention Hall, Room 103

#### BOARD OF REGENTS

Convention Hall, Room 101

Sunday, May 12, 2:00 P.M.

Tuesday, May 14, 12:00 M.\*

Friday, May 17, 12:00 M.\*

#### BOARD OF GOVERNORS

Convention Hall, Room 101

Monday, May 13, 5:00 P.M.

Wednesday, May 15, 12:00 M.\*

\* Buffet luncheon served.

#### SPECIAL FEATURES

Monday, May 13, 1946

**MUSICAL CONCERT BY THE ORPHEUS CLUB OF PHILADELPHIA, WITH SOLOISTS**—There will be no general scientific session on Monday evening, but the Entertainment Committee has arranged a very fine concert by

the famous Orpheus Club of Philadelphia, and by some selected soloists. The concert will be held in the ballroom of the Benjamin Franklin Hotel, at 8:30 o'clock. The Committee firmly believes that this concert will further the social aspects of the College, and hopes it will add greatly to the pleasure of all.

Fellows and Associates, local and visiting physicians and the technical exhibitors, with their families, are invited to attend this concert as guests of the College. The registration badge is all that is needed for identification.

Wednesday, May 16, 1946

**THE VICTORY CONVOCATION OF THE COLLEGE**—8:30 P.M., ballroom, Benjamin Franklin Hotel. All members of the College and their families, and those of the public who are interested, are invited. All physicians elected Fellows of the College since the 1942 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors, and new Fellows to be inducted, are requested to assemble in the Betsy Ross Room, mezzanine floor, Benjamin Franklin Hotel, at 7:45 P.M., preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation promptly at 8:30 P.M. It is suggested that all appear in evening clothes.

The Convocation ceremony will include the President's Address and a Convocational Oration. The award of the John Phillips Memorial Medal for 1946 will be made and the recipients of Research and Clinical Fellowships of the College for 1946 will be announced. The newly elected Fellows will be presented by the Secretary General, Dr. George Morris Piersol, and after subscribing to the Fellowship Pledge, will be inducted by the President. The President's Reception and Dance will follow immediately after the Convocation. All members and their guests are requested to pass along the receiving line.

More than one thousand Fellows are eligible for induction on this occasion, which is being organized as a great Victory Celebration of the College.

Thursday, May 16, 1946

**THE ANNUAL BANQUET** of the College will be held in the ballroom of the Benjamin Franklin Hotel at 8:00 o'clock. The Entertainment Committee is planning a pre-banquet cocktail party for all. Announcements will follow later concerning the speaker of the evening and his title.

All members of the College, physicians of Philadelphia and surrounding area, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will be furnished, and the evening has been planned as a most delightful occasion. Tickets should be purchased at the Registration Bureau by Wednesday afternoon, so that adequate preparations can be consummated.

#### PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Ladies' Entertainment Committee has prepared a delightful program of entertainment for all the visiting women coming to Philadelphia. These guests are asked to register immediately upon arrival in Philadelphia, at the ladies' headquarters at the Benjamin Franklin Hotel. The Ladies' Program will be published later, and a special directory will be provided concerning theaters, stores, restaurants and places of interest in and about Philadelphia.

It will be necessary to make reservations for some of the events on the Ladies' Program; hence the desirability of guests registering promptly on arrival.

## TENTATIVE PROGRAM OF LADIES' ENTERTAINMENT

## MONDAY, MAY 13, 1946

*Morning:* Registration, mezzanine floor, Benjamin Franklin Hotel.

*Afternoon:* Welcoming Tea, Pennsylvania Society of Colonial Dames, 1630 Latimer St.; guests of the Ladies' Entertainment Committee.

*Evening:* 8:30 P.M. Musical Concert by the Orpheus Club of Philadelphia, Ballroom, Benjamin Franklin Hotel.

## TUESDAY, MAY 14, 1946

*Afternoon:* Luncheon at the Headquarters of the American College of Physicians, 4200 Pine St., followed by bus trip to historic Valley Forge.

## WEDNESDAY, MAY 15, 1946

*Afternoon:* Luncheon and Fashion Show by Bonwit Teller, Philadelphia, at the Hotel Barclay, 18th St. and Rittenhouse Sq.

*Evening:* 8:30 P.M. Victory Convocation, followed by President's Reception and Dance, Benjamin Franklin Hotel.

## THURSDAY, MAY 16, 1946

*Afternoon:* Luncheon at the Philadelphia Country Club, West Fairmount Park.

*Evening:* 8:00 P.M. Annual Banquet of the College, Ballroom, Benjamin Franklin Hotel.

**THE TECHNICAL EXHIBIT** will be located on the Exhibition Floor of Convention Hall, 34th Street below Spruce. All exhibit spaces were taken very promptly after distribution of the Invitations; some Exhibitors did not apply in time to obtain space.

The American College of Physicians has steadily raised the standards of Technical Exhibits. All irrelevant products have been eliminated and only firms are invited who present a group of approved products of scientific interest to internal medicine and its allied specialties. Physicians will readily distinguish the difference between this exhibit and general medical exhibits elsewhere, where frequently all sorts of products irrelevant to the actual practice of medicine are displayed and where methods of high pressure selling are common. The exhibit sponsored by our College warrants the respect and interest of every physician. Exhibitors are making a special effort, under current difficult conditions, to present to the members of the College new and improved developments in their respective fields. Here, conveniently available, will be displayed the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your courteous attention, not only because of their educational value, but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions in the general program have been arranged, providing additional time for the inspection of the exhibits.

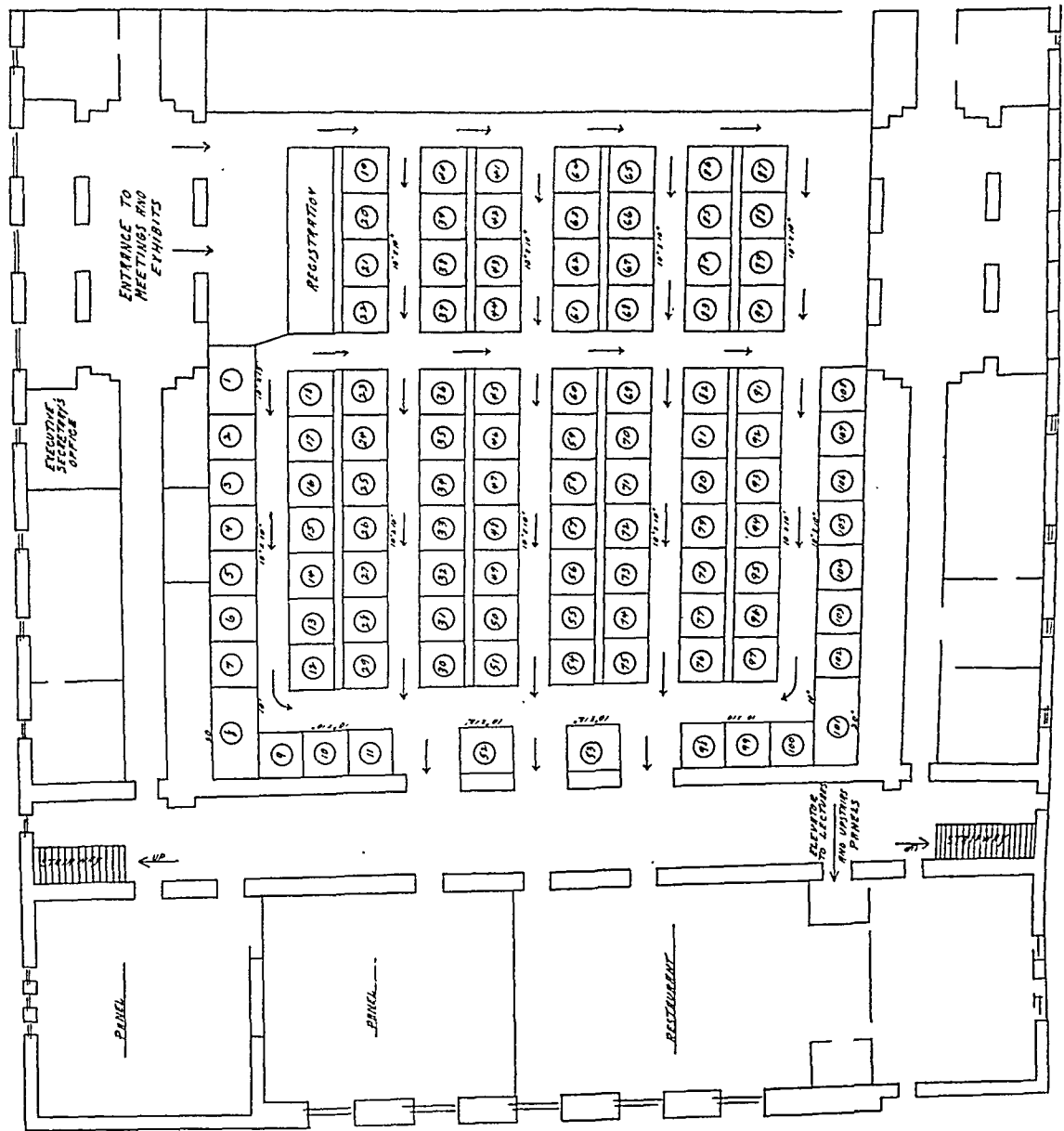
## LIST OF EXHIBITORS

	<i>Booth No.</i>
Abbott Laboratories, North Chicago, Ill. ....	34
American Sterilizer Company, Erie, Pa. ....	96
Ames Company, Inc., Elkhart, Ind. ....	55



Appleton-Century Company, Inc., D., New York, N. Y. ....	60
Arlington Chemical Company, The, Yonkers, N. Y. ....	77
Armour Laboratories, The, Chicago, Ill. ....	83 & 84
Ayerst, McKenna & Harrison Limited, New York, N. Y. ....	16 & 17
Baum Co. Inc., W. A., New York, N. Y. ....	68
Becton, Dickinson & Co., Rutherford, N. J. ....	94 & 95
Bilhuber-Knoll Corp., Orange, N. J. ....	23
Blakiston Company, The, Philadelphia, Pa. ....	53
Borden Company, The, New York, N. Y. ....	37
Bristol Laboratories Inc., Syracuse, N. Y. ....	90
Burdick Corporation, The, Milton, Wis. ....	67
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y. ....	66
Cambridge Instrument Co., Inc., New York, N. Y. ....	108
Cameron Heartometer Company, Chicago, Ill. ....	73
Cameron Surgical Specialty Company, Chicago, Ill. ....	47
Ciba Pharmaceutical Products, Inc., Summit, N. J. ....	49 & 50
Collins, Inc., Warren E., Boston, Mass. ....	99
Cream of Wheat Corporation, The, Minneapolis, Minn. ....	13
Curv-lite Products, Inc., Port Chester, N. Y. ....	74
Davies, Rose & Company, Limited, Boston, Mass. ....	106
Davis Company, F. A., Philadelphia, Pa. ....	36
Dietene Company, Minneapolis, Minn. ....	76
Doak Company, Inc., Cleveland, Ohio ....	89
Doho Chemical Corporation, The, New York, N. Y. ....	63
Electro-Physical Laboratories, Inc., New York, N. Y. ....	97
Emerson Company, J. H., Cambridge, Mass. ....	38
Fleet Company, Inc., C. B., Lynchburg, Va. ....	62
General Electric X-Ray Corporation, Chicago, Ill. ....	58 & 59
Gerber Products Company, Fremont, Mich. ....	78
Gradwohl Laboratories, St. Louis, Mo. ....	51
Grune & Stratton, Inc., New York, N. Y. ....	18
Heinz Co., H. J., Pittsburgh, Pa. ....	100
Hoeber, Inc., Paul B., New York, N. Y. ....	24
Hoffmann-La Roche, Inc., Nutley, N. J. ....	9
Hygeia Nursing Bottle Co., Inc., The, Buffalo, N. Y. ....	104
International Vitamin Corporation, New York, N. Y. ....	14
Jones Metabolism Equipment Co., Chicago, Ill. ....	12
Kellogg Company, Battle Creek, Mich. ....	22
Kidde Manufacturing Co., Inc., Bloomfield, N. J. ....	7
Kinney and Sons, Inc., H. W., Columbus, Ind. ....	103
Knox Gelatine Co., Inc., Chas. B., Johnstown, N. Y. ....	28
LaMotte Chemical Products Company, Baltimore, Md. ....	75
Lea & Febiger, Philadelphia, Pa. ....	41

Lederle Laboratories, Inc., Pearl River, N. Y. ....	8
Lilly and Company, Eli, Indianapolis, Ind. ....	91, 92 & 93
Lippincott Company, J. B., Philadelphia, Pa. ....	61
Macmillan Company, The, New York, N. Y. ....	6
Maltine Company, The, New York, N. Y. ....	72
McNeil Laboratories, Inc., Philadelphia, Pa. ....	15
Mead Johnson & Company, Evansville, Ind. ....	105
Medical Bureau, The, Chicago, Ill. ....	1
Medical Case History Bureau, New York, N. Y. ....	39
Medical Protective Company, Fort Wayne, Ind. ....	21
Merck & Co., Inc., Rahway, N. J. ....	30 & 31
Merrell Company, The Wm. S., Cincinnati, Ohio ....	10 & 11
Mosby Company, The C. V., St. Louis, Mo. ....	44
National Drug Company, The, Philadelphia, Pa. ....	107
Oxford University Press, New York, N. Y. ....	19
Oxygen Equipment Mfg. Corp., New York, N. Y. ....	85
Parke, Davis & Company, Detroit, Mich. ....	52
Patch Company, The E. L., Stoneham, Mass. ....	43
Picker X-Ray Corporation, New York, N. Y. ....	87 & 88
Proctor & Gamble Company, The, Cincinnati, Ohio ....	35
Rare Chemicals, Inc., Harrison, N. J. ....	65
Riedel-de Haen, Inc., New York, N. Y. ....	56
Sanborn Company, Cambridge, Mass. ....	54
Sandoz Chemical Works, Inc., New York, N. Y. ....	48
Saunders Company, W. B., Philadelphia, Pa. ....	40
Schenley Laboratories, Inc., New York, N. Y. ....	101
Schering Corporation, Bloomfield, N. J. ....	32 & 33
Searle & Co., G. D., Chicago, Ill. ....	69, 70 & 71
Sharp & Dohme, Philadelphia, Pa. ....	2, 3, 4 & 5
Smith, Kline & French Laboratories, Philadelphia, Pa. ....	45 & 46
Spencer, Incorporated, New Haven, Conn. ....	64
Squibb & Sons, E. R., New York, N. Y. ....	20
Stearns & Company, Frederick, Detroit, Mich. ....	82
Taylor Instrument Companies, Rochester, N. Y. ....	29
U. S. Vitamin Corporation, New York, N. Y. ....	27
Varick Pharmacal Company, Inc., New York, N. Y. ....	57
Walker & Company, H. W., Chicago, Ill. ....	42
Walker Vitamin Products, Inc., Mount Vernon, N. Y. ....	102
White Laboratories, Inc., Newark, N. J. ....	86
Williams & Wilkins Company, The, Baltimore, Md. ....	98
Winthrop Chemical Company, Inc., New York, N. Y. ....	25 & 26
Wyeth Incorporated, Philadelphia, Pa. ....	79 & 80
Year Book Publishers, Inc., The, Chicago, Ill. ....	81



Floor Plan of Technical Exhibit at Convention Hall.

## OUTLINE OF THE PHILADELPHIA SESSION

Convention Hall events are indicated in bold type.

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	May 13	May 14	May 15	May 16	May 17
9:00 A.M. to 11:30 A.M.	Morning free. Registration, Exhibits, etc.	Hospital Clinics Morning Lectures (9:30-11:30)	Hospital Clinics Morning Lectures (9:30-11:30)	Hospital Clinics Morning Lectures (9:30-11:30)	Hospital Clinics Morning Lectures (9:30-11:30)
12:00 M. to 1:15 P.M.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1:15 P.M. to 2:00 P.M.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:00 P.M. to 5:00 P.M.	1st General Session	2nd General Session	3rd General Session	4th General Session (2:00-4:30) Annual Business Meeting	5th General Session
5:00 P.M. to 8:00 P.M.	Dinner	Dinner	Dinner		
8:00 P.M. to 11:00 P.M.	8:30—Entertainment and Opening Reception	Open Evening for private dinners, etc.	8:30—Convocation followed by President's Reception	Annual Banquet	

## GENERAL SESSIONS PROGRAM

Arena, Convention Hall

## FIRST GENERAL SESSION

Monday Afternoon, May 13, 1946

General Chairman, George Morris Piersol, F.A.C.P., presiding

P.M.

## 2:15 Addresses of Welcome:

The Honorable BERNARD SAMUEL, Mayor of the City of Philadelphia.  
 RUFUS S. REEVES, F.A.C.P., Director of Public Health, City of Philadelphia.  
 J. PARSONS SCHAEFFER, President of the College of Physicians of Philadelphia.  
 LEWIS C. SCHEFFEY, President of the Philadelphia County Medical Society.  
 ROBIN C. BUERKI, F.A.C.P., Dean, University of Pennsylvania Graduate School of Medicine, on behalf of all medical teaching institutions of Philadelphia.

## Response to Addresses of Welcome:

ERNEST E. IRONS, F.A.C.P., President of The American College of Physicians.

## 3:00 INTERMISSION.

President Ernest E. Irons, F.A.C.P., presiding

### MEDICINE IN THE ARMED FORCES; NEW PROBLEMS OF DISEASE AT HOME

## 3:15 The European Theater.

WILLIAM S. MIDDLETON, F.A.C.P., Former Consultant in Medicine, European Theater; Professor of Medicine and Dean, University of Wisconsin Medical School; Madison, Wis.

## 3:30 The Pacific Theater.

HENRY M. THOMAS, JR., F.A.C.P., Former Consultant in Medicine, 1943-1945, Southwestern Pacific Area and AFWESPAC; Associate Professor of Medicine, Johns Hopkins University School of Medicine; Baltimore, Md.

## 3:45 Certain Medical Problems in the Southwest Pacific Area.

MAURICE C. PINCOFFS, F.A.C.P., Former Consultant in Medicine, Southwest Pacific Area, Baltimore, Md.

## 4:00 Streptomycin.

CHESTER S. KEEFER, F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine; Director, Robert Dawson Evans Memorial; and Physician-in-Chief, Massachusetts Memorial Hospitals; Boston, Mass.

## 4:30 Penicillin in Neurosyphilis.

GEORGE D. GAMMON, F.A.C.P., Professor of Clinical Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pa.;  
 JOHN H. STOKES (by invitation), Emeritus Professor of Cutaneous Medicine and Syphilology, University of Pennsylvania School of Medicine; Philadelphia, Pa.;

And Members of the Penicillin Syphilis Panel of the Hospital of the University of Pennsylvania.

5:00 ADJOURNMENT.

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## SECOND GENERAL SESSION

Tuesday Afternoon, May 14, 1946

Presiding Officer

David P. Barr, F.A.C.P., New York, N. Y.

## SYMPOSIUM ON PLASMA FRACTIONS

P.M.

2:00 **The Separation of Blood into Fractions of Therapeutic Value (1946 John Phillips Medalist Presentation).**

EDWIN J. COHN (by invitation), Professor of Biological Chemistry and Head, Department of Physical Chemistry, Harvard Medical School, Boston, Mass.

2:40 **Clinical Studies with Gamma Globulin.**

JOSEPH STOKES, JR. (by invitation), William H. Bennett Professor of Pediatrics, University of Pennsylvania School of Medicine; Medical Director, Children's Hospital; Philadelphia, Pa.

2:55 **Antihemophilic Globulin.**

GEORGE R. MINOT, F.A.C.P., Professor of Medicine, Harvard Medical School; Director, Thorndike Memorial Laboratory; Boston, Mass.;

F. H. LASKEY TAYLOR (by invitation), Associate in Research Medicine, Harvard Medical School, Boston, Mass.

3:10 **Other Clinical Uses of Blood Derivatives.**

CHARLES A. JANEWAY (by invitation), Assistant Professor of Pediatrics, Harvard Medical School, Boston, Mass.

3:25 INTERMISSION.

3:50 **Factors Affecting the Growth of Tubercle Bacilli.**

RENÉ J. DUBOS, Ph.D. (by invitation), Member, The Rockefeller Institute for Medical Research, New York, N. Y.;

BERNARD D. DAVIS (by invitation), Visiting Investigator, The Rockefeller Institute for Medical Research; Senior Assistant Surgeon, Tuberculosis Control Division, U. S. Public Health Service; New York, N. Y.

4:05 **Immunological Reactions with Tubercle Bacilli.**

GARDNER MIDDLEBROOK (by invitation), Assistant, The Rockefeller Institute for Medical Research, New York, N. Y.;

RENÉ J. DUBOS, Ph.D. (by invitation), New York, N. Y.

4:20 **The Anoxemia Test for Coronary Insufficiency.**

LOUIS F. BISHOP, JR., F.A.C.P., Visiting Physician, Bellevue Hospital, New York, N. Y.;

HENRY J. WEINTRAUB (by invitation), Mount Sinai Hospital, New York, N. Y.

4:35 **Pulmonary Embolism.**

SIMON S. LEOPOLD, F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

4:50 **ADJOURNMENT.**


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**THIRD GENERAL SESSION**

Wednesday Afternoon, May 15, 1946

Presiding Officer

Walter W. Palmer, F.A.C.P., New York, N. Y.

P.M.

2:00 **Geriatrics.**

ROGER I. LEE, F.A.C.P., Fellow, Harvard University; President, American Medical Association; Boston, Mass.

2:20 **Reflex Sympathetic Dystrophy.**

JAMES A. EVANS, F.A.C.P., Physician, Lahey Clinic, Boston, Mass.

2:40 **Psychogenic Rheumatism.**

EDWARD WEISS, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia, Pa.

3:00 **Rehabilitation: War Time Lessons Applied to Peace Time Needs.**

HOWARD A. RUSK, F.A.C.P., Instructor in Medicine, Washington University School of Medicine, St. Louis, Mo.

3:15 **INTERMISSION.**3:40 **Section of the Vagus Nerve to the Stomach in the Treatment of Peptic Ulcer.**

LESTER R. DRAGSTEDT, F.A.C.P., Professor of Surgery, University of Chicago, The School of Medicine, Chicago, Ill.

4:00 **Treatment of Peptic Ulcer by Histamine.**

BENJAMIN M. BERNSTEIN, F.A.C.P., Instructor, Division of Home Economics, New York University; Chief, Division of Gastro-enterology, Jewish Hospital; Brooklyn, N. Y.

4:20 **Continuous Fever: Segmental Colitis.**

BURRILL B. CROHN, F.A.C.P., Associate in Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

4:40 **Hepatic Cirrhosis as a Complication of Ulcerative Colitis.**

HENRY J. TUMEN, F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine; Associate in Medicine, Temple University School of Medicine; Philadelphia, Pa.;

J. F. MONAGHAN (by invitation), Associate in Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.;

EMIL JOBB (by invitation), Assistant Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

5:00 **ADJOURNMENT.**

**FOURTH GENERAL SESSION**

Thursday Afternoon, May 16, 1946

Presiding Officer

James J. Waring, F.A.C.P., Denver, Colo.

P.M.

**2:00 Use of Thiouracil in Hyperthyroidism.**

E. B. ASTWOOD (by invitation), Research Professor of Medicine, Tufts College Medical School; Endocrinologist, Joseph H. Pratt Diagnostic Hospital; Boston, Mass.

**2:20 A Critical Comparison of Available Methods of Treatment of Graves' Disease.**

JAMES HOWARD MEANS, F.A.C.P., Jackson Professor of Clinical Medicine, Harvard Medical School, Boston, Mass.

**2:40 Epidemic Hepatitis.**

RICHARD B. CAPPS, F.A.C.P., Associate in Medicine, Northwestern University Medical School, Chicago, Ill.

**3:00 INTERMISSION.****3:20 Prescription of Physical Medicine by the Internist.**

ARTHUR L. WATKINS (by invitation), Associate in Medicine, Harvard Medical School; Chief of Physical Medicine, Massachusetts General Hospital; Boston, Mass.

**3:40 Diagnosis of Occupational Disease.**

IRVING GRAY, F.A.C.P., Attending Physician, Coney Island, Seaview and Harbor Hospitals, Brooklyn, N. Y.

**4:00 Brucella Sensitization: A Clinical Evaluation.**

WARD DARLEY, JR., F.A.C.P., Dean and Professor of Medicine, University of Colorado School of Medicine, Denver, Colo.;  
ROBERT W. GORDON, F.A.C.P., Instructor in Medicine, University of Colorado School of Medicine, Denver, Colo.

**4:20 ADJOURNMENT.****4:30 THE ANNUAL BUSINESS MEETING.**

All Masters and Fellows are urged to be present. Annual reports of the Secretary General, Executive Secretary and Treasurer will be presented; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. David P. Barr, New York, N. Y., will be inducted into office.

**FIFTH GENERAL SESSION**

Friday Afternoon, May 17, 1946

Presiding Officer

C. W. Dowden, F.A.C.P., Louisville, Ky.

P.M.

**2:00 Tsutsugamushi Disease (Scrub Typhus): A Review of Recent Observations.**

FRANCIS G. BLAKE, F.A.C.P., Sterling Professor of Medicine and Dean, Yale University School of Medicine; Physician-in-Chief, New Haven Hospital; New Haven, Conn.



**2:20 Vectors of Rickettsial Diseases.**

GLEN M. KOHLS (by invitation), Lt. Col., Sanitary Corps, AUS; Member, American Typhus Commission; Entomologist, Rocky Mountain Laboratory, U. S. Public Health Service; Washington, D. C.

**2:35 Colorado Tick Fever.**

EDWARD R. MUGRAGE, F.A.C.P., Professor and Head of Department, Public Health and Laboratory Diagnosis, University of Colorado School of Medicine, Denver, Colo.;

LLOYD FLORIO (by invitation), Associate Professor of Public Health and Laboratory Diagnosis, University of Colorado School of Medicine, Denver, Colo.;

MABEL O. STEWART, B.S. (by invitation), Instructor in Medical Technology (Laboratory Diagnosis), University of Colorado School of Medicine, Denver, Colo.

**2:50 The Use of Folic Acid in Sprue.**

RAMÓN M. SUÁREZ, F.A.C.P., Associate Professor of Tropical Medicine and Head of Department of Clinical Medicine, School of Tropical Medicine of the University of Puerto Rico, Columbia University; Governor of The American College of Physicians; San Juan, P. R.;

TOM D. SPIES, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine; Director, Nutrition Clinic, Hillman Hospital of Birmingham; Cincinnati, Ohio, and Birmingham, Ala.;

RAMÓN M. SUÁREZ, JR. (by invitation), San Juan, P. R.

**3:05 Globin Insulin and Protamine Zinc Insulin: A Comparison of Their Use in Equal Doses.**

JOSEPH T. ROBERTS (Associate), Adjunct Clinical Professor of Medicine, Georgetown University School of Medicine and George Washington University School of Medicine; Chief Medical Officer, Department of Medicine, Gallinger Municipal Hospital; Washington, D. C.;

WALLACE M. YATER, F.A.C.P., Civilian Consultant, Army Institute of Pathology; Governor of The American College of Physicians; Washington, D. C.

**3:20 INTERMISSION.****3:30 Immunization against Influenza.\***

THOMAS FRANCIS, JR. (by invitation), Professor of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Mich.;

JONAS E. SALK (by invitation), Research Associate in Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Mich.

**3:45 Immobilization of Both Lungs in the Treatment of Pulmonary Tuberculosis.**

ALVAN L. BARACH, F.A.C.P., Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

**4:00 Influence of Alkalies and Other Adjuvants in Prevention and Control of Sulfonamide Crystalluria.**

HARRISON F. FLIPPIN, F.A.C.P., Visiting Physician, Philadelphia General Hospital, Philadelphia, Pa.;

JOHN G. REINHOLD, Ph.D. (by invitation), Principal Biochemist, Philadelphia General Hospital, Philadelphia, Pa.

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\* Studies largely supported by Commission on Influenza, Army Epidemiological Board.

**4:15 The Element of Bronchial Spasm in Heart Failure.**

MILTON PLOTZ, F.A.C.P., Assistant Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

**4:30 ADJOURNMENT.**

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**MORNING LECTURES**

The Morning Lectures fulfill the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures, however, are organized to give the speaker adequate time to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge.

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**Tuesday, May 14, 1946**

**Ballroom, Convention Hall**

**Presiding Officer**

**Hugh J. Morgan, F.A.C.P., Nashville, Tenn.**

**A.M.**

**9:30-10:20 Blood Banks and Storage of Blood.**

MAX M. STRUMIA, F.A.C.P., Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine; Director, Laboratory of Clinical Pathology, Bryn Mawr Hospital; Bryn Mawr, Pa.

**10:20-10:30 Intermission.****10:30-11:30 The Management of Renal Dysfunction.**

JOHN EIMAN, F.A.C.P., Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine; Director, Department of Pathology, Abington Memorial Hospital; Abington, Pa.;

C. G. GROSSCUP, Ph.D. (by invitation) and

C. W. SCULL, Ph.D. (by invitation), Biochemists, Abington Memorial Hospital, Abington, Pa.

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**Wednesday, May 15, 1946**

**Ballroom, Convention Hall**

**Presiding Officer**

**LeRoy H. Sloan, F.A.C.P., Chicago, Ill.**

**A.M.**

**9:30-10:20 Nitrogen Metabolism in Chronic Disease.**

JONATHAN C. MEAKINS, F.A.C.P., Dean and Professor of Medicine, McGill University Faculty of Medicine; Physician-in-Chief, Royal Victoria Hospital; Montreal, P.Q., Can.;

J. S. L. BROWNE (by invitation), Associate Professor of Medicine,  
McGill University Faculty of Medicine, Montreal, P.Q., Can.;  
VICTOR SCHENKER, Ph.D. (by invitation), Research Fellow, McGill  
University Faculty of Medicine, Montreal, P.Q., Can.

10:20-10:30 Intermission.

10:30-11:30 Liver Function in Hepatitis.

CECIL J. WATSON, F.A.C.P., Professor of Medicine, University of  
Minnesota Medical School, Minneapolis, Minn.

Thursday, May 16, 1946

Ballroom, Convention Hall

Presiding Officer

George F. Strong, F.A.C.P., Vancouver, B. C., Can.

A.M.

9:30-10:20 Schistosomiasis.

ERNEST CARROLL FAUST (by invitation), Professor of Parasitology  
and Acting Head of Department of Tropical Medicine, Tulane Uni-  
versity of Louisiana School of Medicine, New Orleans, La.

10:20-10:30 Intermission.

10:30-11:30 Diverticula of the Gastrointestinal Tract.

WALTER L. PALMER, F.A.C.P., Professor of Medicine, University of  
Chicago, The School of Medicine; Governor of The American Col-  
lege of Physicians; Chicago, Ill.

Friday, May 17, 1946

Ballroom, Convention Hall

Presiding Officer

T. Z. Cason, F.A.C.P., Jacksonville, Fla.

A.M.

9:30-10:20 Coronary Artery Disease in 18-39 Year Age Group (A Study of  
800 Cases).

WALLACE M. YATER, F.A.C.P., Civilian Consultant, Army Institute  
of Pathology; Governor of The American College of Physicians;  
Washington, D. C.;

AARON H. TRAUM, Major, (MC), AUS (by invitation), Chief, Cardio-  
vascular Research Unit, Veterans Administration Hospital, Washing-  
ton, D. C.;

WILSON G. BROWN, Major, (MC), AUS (by invitation), Pathologist,  
Army Institute of Pathology, Washington, D. C.

10:20-10:30 Intermission.

**10:30-11:30 Peripheral Vascular Disease.**

IRVING S. WRIGHT, F.A.C.P., Professor of Clinical Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, New York, N. Y.

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**PANEL DISCUSSIONS**

The Panel Discussions embrace not only timely subjects, but also topics of the greatest interest and practical nature to the profession. Only highly qualified men in their respective fields have been chosen as leaders, and they in turn will select their own personnel. For the most part the discussers will be gathered from various parts of the country in order to secure the best talent available for each Panel. Listeners should be able to receive the latest as well as the most orthodox views and opinions on the subject under discussion.

Panel Discussions will be held in the Convention Hall from 12:00 M. to 1:15 P.M. daily—Tuesday through Friday.

When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. Questions may also be submitted at least twenty-four hours before the discussion to the General Chairman. A certain number of these request questions may not be answered on account of lack of time. Leaders will answer those questions which seem to be most in demand.

*Members should make application for Panel Tickets on the regular application form accompanying the formal program or at the Registration Bureau at Convention Hall.*

**PROGRAM OF PANEL DISCUSSIONS**

**Tuesday, May 14, 1946**

**Convention Hall**

**Ballroom, 3d Floor**

**I (Capacity, 800)**

**12:00 M.-1:15 P.M. Antibiotic Therapy.**

CHESTER S. KEEFER, F.A.C.P., Boston, Mass.

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**Convention Hall**

**Room 300, Ballroom Extension, 3d Floor**

**II (Capacity, 275)**

**12:00 M.-1:15 P.M. Treatment of Thyroid Disease.**

JAMES HOWARD MEANS, F.A.C.P., Boston, Mass.

## Convention Hall

Room 200, Lobby Lounge, Arena Floor

III (Capacity, 250)

12:00 M.-1:15 P.M. Treatment of Liver Disease.

CECIL J. WATSON, F.A.C.P., Minneapolis, Minn.

## Convention Hall

Room 305, 3d Floor, North

IV (Capacity, 100)

12:00 M.-1:15 P.M. Tropical Medicine in General Practice.

MAURICE C. PINCOFFS, F.A.C.P., Baltimore, Md.

## PANEL DISCUSSIONS

Wednesday, May 15, 1946

## Convention Hall

Ballroom, 3d Floor

V (Capacity, 800)

12:00 M.-1:15 P.M. Medical Viewpoints of Cardiovascular Surgery.

PAUL D. WHITE, F.A.C.P., Boston, Mass.

## Convention Hall

Room 300, Ballroom Extension, 3d Floor

VI (Capacity, 275)

12:00 M.-1:15 P.M. Treatment of Syphilis.

JOHN H. STOKES (by invitation), Philadelphia, Pa.

## Convention Hall

Room 200, Lobby Lounge, Arena Floor

VII (Capacity, 250)

12:00 M.-1:15 P.M. Electrocardiography.

CHARLES C. WOLFERTH, F.A.C.P., Philadelphia, Pa.

## Convention Hall

Room 305, 3d Floor, North

VIII (Capacity, 100)

12:00 M.-1:15 P.M. Treatment of Peptic Ulcer.

T. GRIER MILLER, F.A.C.P., Philadelphia, Pa.

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PANEL DISCUSSIONS

Thursday, May 16, 1946

## Convention Hall

Ballroom, 3d Floor

IX (Capacity, 800)

12:00 M.-1:15 P.M. Treatment of Hypertension.

R. H. SMITHWICK (by invitation), Boston, Mass.

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Convention Hall

Room 300, Ballroom Extension, 3d Floor

X (Capacity, 275)

12:00 M.-1:15 P.M. Diabetes.

ELLIOTT P. JOSLIN, F.A.C.P., Boston, Mass.

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Convention Hall

Room 200, Lobby Lounge, Arena Floor

XI (Capacity, 250)

12:00 M.-1:15 P.M. Allergy.

RICHARD A. KERN, F.A.C.P., Philadelphia, Pa.

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Convention Hall

Room 305, 3d Floor, North

XII (Capacity, 100)

12:00 M.-1:15 P.M. Peripheral Vascular Disease.

EDGAR V. ALLEN, F.A.C.P., Rochester, Minn.

## PANEL DISCUSSIONS

Friday, May 17, 1946

Convention Hall

Ballroom, 3d Floor

XIII

(Capacity, 800)

12:00 M.-1:15 P.M. Arthritis.

RUSSELL L. CECIL, F.A.C.P., New York, N. Y.

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 Convention Hall

Room 300, Ballroom Extension, 3d Floor

XIV

(Capacity, 275)

12:00 M.-1:15 P.M. Hematology.

O. H. PERRY PEPPER, F.A.C.P., Philadelphia, Pa.

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 Convention Hall

Room 200, Lobby Lounge, Arena Floor

XV

(Capacity, 250)

12:00 M.-1:15 P.M. Blood Transfusion and Blood Substitutes

MAX M. STRUMIA, F.A.C.P., Bryn Mawr, Pa.

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 Convention Hall

Room 305, 3d Floor, North

XVI

(Capacity, 100)

12:00 M.-1:15 P.M. Vitamins.

JULIAN M. RUFFIN, F.A.C.P., Durham, N. C.

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 THE CLINIC SESSIONS

The program of the Clinic Sessions—Tuesday to Friday, inclusive, from 9:00 A.M. to 11:30 A.M.—has been modeled on those which have proved so successful in past years. Emphasis has been placed on clinics in the true sense of that word and there is scarcely a field of medicine which is not represented on the program. In addition to the various aspects of internal medicine, there are ample offerings in the subjects of pediatrics, psychiatry, neurology, roentgenology, as well as in certain more distant fields which are still of importance to the internist, as for example bronchoscopy, carcinoma and certain surgical subjects. Ample opportunities in ward walks are offered for those who wish to see patients at close range and observe hospital methods in Philadelphia. Scientific demonstrations are offered on some programs that the visitors may see the research work actually being carried on at this time in the various laboratories.

The clinic program offers daily a capacity of over 2,500, scattered over fourteen hospitals as well as some of the medical schools of the city.

*Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations unless specifically otherwise mentioned.* The coöperation of everyone in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each program. It is self-evident that a ward round arranged for fifteen will lose its value for all if forty or fifty are present. Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated.

To all members of the College, registration blanks for the clinics and demonstrations will be distributed with the program.

## PROGRAM OF CLINICS

Tuesday, May 14, 1946

A

### CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Nurses' Home, Auditorium

(Capacity, 75)

- 9:00- 9:30 Care of the Premature Infant. Demonstration.  
C. C. CHAPPLE.
- 9:30-10:00 The Handling of Behavior Problems in Pediatric Practice.  
SHERMAN LITTLE.
- 10:00-10:30 Discussion and Demonstration of Immune and Susceptible Responses to Skin Tests in Pertussis. Demonstration.  
A. C. MCGUINNESS.
- 10:30-11:00 Clinic on Nephrosis.  
MILTON RAPOPORT.
- 11:00-11:30 The Methods of Clinical Application of Rh Testing. Demonstration.  
NEVA ABELSON.

B

### GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 100)

- 9:00- 9:30 Clinic: Gastro-enterology.  
H. L. BOCKUS.
- 9:30-10:10 Clinic: Peptic Ulcer.  
SARA M. JORDAN, Boston, Mass.
- 10:10-10:50 Clinic: Gastro-enterology.  
WALTER L. PALMER, Chicago, Ill.
- 10:50-11:30 Clinic: Pediatric Gastro-enterology  
JOSEPH A. RITTER.



Tuesday, May 14, 1946 (continued)

**C HAHNEMANN MEDICAL COLLEGE AND HOSPITAL**

(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 175)

- 9:00-10:00 Treatment of Congestive Heart Failure.  
G. HARLAN WELLS.
- 10:00-10:45 Diabetes Mellitus.  
E. ROLAND SNADER, JR.
- 10:45-11:30 Rheumatic Heart Disease.  
GEORGE D. GECKELER.

**D-1****HOSPITAL OF THE UNIVERSITY  
OF PENNSYLVANIA**

(36th and Spruce Streets)

Medical Amphitheatre

(Capacity, 200)

- 9:30-10:00 Thyroid Disease and Associated Ocular Disturbances.  
JAMES H. MEANS, Boston, Mass.
- 10:00-10:30 Pheochromocytoma of the Adrenal with Paroxysmal Hypertension.  
ROBERT L. MAYOCK.
- 10:30-11:00 Anorexia Nervosa.  
F. W. SUNDERMAN.
- 11:00-11:30 Ovarian Hypogenesis Associated with Retarded Skeletal Growth and  
other Congenital Anomalies.  
W. H. PERLOFF.

**D-2****UNIVERSITY OF PENNSYLVANIA  
MEDICAL SCHOOL BUILDING**

(36th Street and Hamilton Walk)

Lecture Room, Medical Laboratories

(Capacity, 213)

- 9:30-10:00 Roentgen Diagnosis of Pulmonary Suppurative Lesions.  
PHILIP J. HODES.
- 10:00-10:30 The Surgical Management of Pulmonary Suppuration.  
JULIAN JOHNSON.
- 10:30-11:00 Roentgen Therapy for Metastatic Malignancy.  
EUGENE P. PENDERGRASS.
- 11:00-11:30 The Relief of Pain.  
FRANCIS C. GRANT.

Tuesday, May 14, 1946 (continued)

F-1

**JEFFERSON HOSPITAL**

(10th and Sansom Streets)

Clinical Amphitheatre, 1st Floor

(Capacity, 300)

**CLINIC**

- 9:00- 9:40 Anemias.  
HAROLD W. JONES.
- 9:40-10:30 Leukemias.  
FRANKLIN R. MILLER.
- 10:30-10:40 INTERMISSION.
- 10:40-11:30 Hemolytic Diseases.  
LEANDRO M. TOCANTINS.

F-2

**JEFFERSON MEDICAL COLLEGE**

(1025 Walnut Street)

Society Room

(Capacity, 96)

**DEMONSTRATIONS**

- 9:00-11:00 Endocrines.  
ABRAHAM E. RAKOFF.

F-3

**JEFFERSON MEDICAL COLLEGE**

(1025 Walnut Street)

Room 310

(Capacity, 80)

**DEMONSTRATIONS**

- 9:00-11:00 Rh Factor.  
LOWELL A. ERF.

H-1

**LANKENAU HOSPITAL**

(Corinthian and Girard Avenues)

Nurses' Auditorium

(Capacity, 200)

- 9:00- 9:20 Unusual Case of Leukemia with Comments on Fever Therapy.  
FREDERICK L. HARTMANN.
- 9:20- 9:40 Aneurysms of the Renal Artery.  
CHARLES UHLE.
- 9:40-10:00 Sensitivity to Diodrast.  
ARTHUR SINGER.
- 10:00-10:15 Otosclerosis—Modern Treatment.  
EDWARD H. CAMPBELL.

Tuesday, May 14, 1946 (continued)

- 10:15-10:30 Nasal Allergy.  
LOUIS E. SILCOX.
- 10:30-11:30 Diabetic Clinic.  
ELLIOTT P. JOSLIN, Boston, Mass.

H-2

**LANKENAU HOSPITAL**  
(Corinthian and Girard Avenues)  
**Surgical Amphitheatre**  
(Capacity, 100)

- 9:00- 9:20 Living with a Colostomy.  
ALBERT G. MARTIN.
- 9:20- 9:40 Problems of Reconstructive Surgery.  
HANS MAY.
- 9:40-10:00 Psychoneurosis in Ex-Service Men.  
FREDERIC H. LEAVITT.
- 10:00-10:30 Hepatitis.  
W. PAUL HAVENS, New Haven, Conn.
- 10:30-11:30 Clinic on Arthritis.  
RUSSELL L. CECIL, New York, N. Y.

H-3

**LANKENAU HOSPITAL**  
(Corinthian and Girard Avenues)  
**Research Institute**  
(Capacity, 35)

- 9:00- 9:15 Bacterial Products and Cancer.  
I. C. DILLER.
- 9:15- 9:30 Protozoa and Cancer.  
T. S. HAUSCHKA.
- 9:30- 9:45 Immunological Reactions to Carcinogens and Bacterial Products.  
H. G. CREECH.
- 9:45-10:00 Pathology of Experimental Tumors.  
ROBERT W. BRIGGS.
- 10:00-10:15 Cultures of Plant and Animal Cancer Cells.  
PHILLIP R. WHITE.
- 10:15-10:30 The Chromosomes of Man.  
JACK SCHULTZ.
- 10:30-10:45 Methods of Anti-Cancer Education for the Public.  
STANLEY P. REIMANN.
- 10:45-11:00 Nutritional Factors in Cancer Patients.  
MARY A. BENNETT.
- 11:00-11:15 Tissue Proteins in Human Cancer.  
GERRIT TOENNIES.
- 11:15-11:30 The Use of Isotopes in Medicine.  
GRACE MEDES.

Tuesday, May 14, 1946 (continued)

**PENNSYLVANIA HOSPITAL**

(8th and Spruce Streets)

**Auditorium**

(Capacity, 100)

- J
- 9:30-10:10 The Heart in Pregnancy.  
MORRIS W. STROUD, III.
- 10:10-10:50 The Human Assay of Digitalis-like Preparations.  
J. A. WAGNER.
- 10:50-11:30 Congenital Heart Disease, with Demonstration.  
M. A. GOLDSMITH.

**K PHILADELPHIA GENERAL HOSPITAL**

(34th Street below Spruce)

**Nurses' Auditorium**

(Capacity, 200)

- 9:00- 9:50 Pulmonary Dyspnea versus Cardiac Dyspnea.  
WILLIAM S. McCANN, Rochester, N. Y.
- 9:50-10:15 Studies of Causative Agents in Hepatitis.  
JOSEPH STOKES, JR.
- 10:15-10:40 Application of Liver Functional Tests in Infectious Hepatitis.  
JOHN G. RHEINHOLD.
- 10:40-11:30 Clinical Pathological Conference.  
HUGH J. MORGAN, Nashville, Tenn.  
WILLIAM E. EHRLICH.

**L-1 PRESBYTERIAN HOSPITAL**

(39th Street and Powelton Avenue)

**Gymnasium**

(Capacity, 150)

- 9:00- 9:30 Methemoglobinuria and Its Treatment with Vitamin C.  
THOMAS KLEIN.
- 9:30-10:00 Mononucleosis.  
JAMES E. COTTRELL.
- 10:00-10:30 Rupture of the Spleen in Mononucleosis (seven cases).  
R. PHILIP CUSTER.
- 10:30-11:00 Morbidity in Transfusions: Study of One Thousand Consecutive Cases.  
JOHN W. HOOKER.
- 11:00-11:30 Sympathectomy and Hypertension: Presentation of Cases.  
F. A. BOTHE.

Tuesday, May 14, 1946 (continued)

M-1

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

(3400 N. Broad Street)

Medical School Building, Room 316

(Capacity, 400)

Symposium on "Antibiotic Therapy."

JOHN A. KOLMER, *Presiding*.

- 9:00- 9:30 The Laboratory Aspects of Antibiotic Therapy.  
EARLE H. SPAULDING.  
AMEDEO BONDI, JR.
- 9:30-10:00 Penicillin Inhalation Therapy.  
CHARLES M. NORRIS.
- 10:00-10:30 Penicillin in the Treatment of Bacterial Endocarditis.  
JOHN A. KOLMER.
- 10:30-11:00 The Pharmacology and Clinical Applications of Streptomycin.  
JOHN A. KOLMER.
- 11:00-11:30 Questions and Discussion.

M-2

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

(3400 N. Broad Street)

X-Ray Museum, 6th Floor

(Capacity, 90)

Cardiac Clinics.

CHARLES L. BROWN, *Presiding*.

- 9:00- 9:30 Air Embolism and Its Treatment.  
THOMAS M. DURANT.
- 9:30-10:00 Heart Disease Complicated by Pregnancy: Case Demonstration.  
GEORGE E. MARK, JR.
- 10:00-10:30 Plea for Early Surgical Treatment of Constrictive Pericarditis: Case  
Demonstration.  
I. W. GINSBURG.
- 10:30-11:30 Electrocardiography: A Method of Recording the Movements of the  
Heart and Great Vessels.  
W. EDWARD CHAMBERLAIN.  
M. J. OPPENHEIMER.  
BERT R. BOONE.  
GEORGE C. HENNY.  
FREDERICK GILLICK.

N

UNITED STATES NAVAL HOSPITAL

(Broad Street and Pattison Avenue)

Library Seminar Room

(Capacity, 36)

Captain WALTER H. SCHWARTZ, (MC), USN, *Chairman*.

- 9:30-10:00 Clinical Malaria and Relapse.

**Tuesday, May 14, 1946 (continued)**

- 10:00-10:30 Peptic Ulcer in Young Service Personnel.  
 10:30-11:00 Amebic Liver Abscess.  
 11:00-11:30 Physical Medicine: Clinic and Demonstration.

**Transportation will be furnished by Navy bus**

(Courtesy of Captain M. J. ASTON, (MC), USN, Medical  
 Officer in Command, U. S. Naval Hospital)

Leave: Benjamin Franklin Hotel at 8:50 A.M.

Leave: Bellevue-Stratford Hotel at 9:00 A.M.

Return: Following the Clinics, directly to Convention Hall.

O

**WOMAN'S MEDICAL COLLEGE  
 OF PENNSYLVANIA**

**Philadelphia General Hospital**

**(34th Street below Spruce)**

**Surgical Amphitheatre**

**(Capacity, 225)**

- 9:00-10:00 Modern Concepts in the Treatment of Congestive Cardiac Failure.  
 GEORGE HERRMANN, Galveston, Tex.  
 SAMUEL BELLET.  
 WILLIAM G. LEAMAN, JR.
- 10:00-11:30 Problems in the Management of Coronary Artery Disease.  
 ROBERT L. LEVY, New York, N. Y.  
 WILLIAM D. STROUD.  
 REGINALD FITZ, Boston, Mass.

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**Wednesday, May 15, 1946**

A

**CHILDREN'S HOSPITAL**

**(18th and Bainbridge Streets)**

**Nurses' Home, Auditorium**

**(Capacity, 75)**

- 9:00- 9:30 Adequate Basis for Cardiologic Diagnoses in Rheumatic Fever.  
 T. N. HARRIS.
- 9:30-10:00 Discussion of Methods and Value of Vaccination against Epidemic  
 Influenza.  
 WERNER HENLE.
- 10:00-10:30 Nutritional Factors in Ectoparasitic Infections. Motion Picture.  
 PAUL GYORGY.
- 10:30-11:00 Skin Tests for Immunity and Susceptibility in Mumps. Demonstration.  
 ELIZABETH MARIS.
- 11:00-11:30 Clinic: Diarrheal Problems.  
 JOHN P. SCOTT.

Wednesday, May 15, 1946 (continued)

B

GRADUATE HOSPITAL OF THE  
UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 100)

- 9:00- 9:25 Clinic: Congenital Heart Disease.  
SAMUEL BELLET.
- 9:25- 9:45 Surgical Aspects.  
HERBERT R. HAWTHORNE.
- 9:45-10:30 Cardiovascular Clinic.  
WILLIAM D. STROUD.
- 10:30-11:30 Digitalis Preparations and Their Use.  
HARRY GOLD, New York, N. Y.

C HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 175)

- 9:00-10:45 Use of Electroencephalograms in Convulsive Disorders of Childhood.  
CARL C. FISCHER.  
CUNLIFFE BARNES.
- 10:45-11:30 Diagnostic Value of Bronchography. (Illustrative Cases).  
J. ANTRIM CRELLIN.

D-1

HOSPITAL OF THE UNIVERSITY  
OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Amphitheatre

(Capacity, 200)

- 9:15- 9:45 Nutrition.  
JOHN B. YOUNG, Nashville, Tenn.
- 9:45-10:15 The Action of a Tumor Virus in Vitro.  
DALE R. COMAN.
- 10:15-11:30 Pathological Seminar.  
O. H. PERRY PEPPER and STAFF.

D-2

UNIVERSITY OF PENNSYLVANIA  
MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room, Medical Laboratories

(Capacity, 213)

- 9:30-10:00 Diet in the Jaundiced Patient.  
I. S. RAVDIN.

Wednesday, May 15, 1946 (continued)

- 10:00-10:30 Parathyroid Adenomata.  
HENRY P. ROYSTER.
- 10:30-11:00 Gelatin as a Plasma Substitute.  
C. E. KOOP.
- 11:00-11:30 Cicatrizing Enterocolitis.  
L. KRAEER FERGUSON.

E THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL  
(111 N. 49th Street)

Auditorium

(Capacity, 250)

- 9:00- 9:20 Lessons Learned from World War II for Civilian Psychiatry.  
ELWARD A. STRECKER.
- 9:20- 9:40 Some Psychodynamic Aspects of Battle Reactions.  
CALVIN S. DRAYER.  
EDWIN A. WEINSTEIN.
- 9:40-10:00 Epilepsy and Behavior Disorders.  
JOSEPH HUGHES.
- 10:00-10:20 Observations on the Use of Tridione.  
WILLIAM C. WERMUTH.  
RACHEL B. WOODFORD.
- 10:20-10:40 The Present Status of Insulin Therapy.  
JAY SHURLEY.
- 10:40-11:00 Electroshock Therapy with the Use of Pentothal.  
WILLIAM C. WERMUTH.  
JOHN EICHHOLTZ.
- 11:00-11:20 Hyper-secretory Syndromes in the Neuroses.  
PIERRE SIMONART.

F-1

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Clinical Amphitheatre, 1st Floor

(Capacity, 300)

CLINIC

- 9:00- 9:40 Minor Respiratory Tract Infections.  
HOBART A. REIMANN.
- 9:40-10:30 (Clinic to be announced).
- 10:30-10:40 INTERMISSION.
- 10:40-11:30 Pneumonias.  
HOBART A. REIMANN.



Wednesday, May 15, 1946 (continued)

F-2

**JEFFERSON HOSPITAL**

(10th and Sansom Streets)

Clinical Laboratory

(Capacity, 50)

**DEMONSTRATION**

9:00-11:00 Transfusion Unit.  
LOWELL A. ERF.

F-3

**JEFFERSON MEDICAL COLLEGE**

(1025 Walnut Street)

Physiology Laboratory, 4th Floor

(Capacity, 30)

**DEMONSTRATION**

9:00-11:00 Intestinal Parasites.  
WILLIAM G. SAWITZ.

G

**JEWISH HOSPITAL**

(York and Tabor Roads)

Medical Wards

(Capacity, 20)

9:30-10:30 Treatment of Barbiturate Poisoning.  
NATHAN BLUMBERG.

10:30-11:30 Demonstrations of Modern Methods of Diagnosis and Treatment of  
Peripheral Vascular Diseases.  
JOSEPH C. DOANE.

H-1

**LANKENAU HOSPITAL**

(Corinthian and Girard Avenues)

Nurses' Auditorium

(Capacity, 200)

9:00- 9:20 Prophylaxis in Geriatrics.  
EDWARD L. BORTZ.

9:20- 9:40 Adrenal Tumors with Paroxysmal Hypertension (4 cases).  
NICHOLAS PADIS.

9:40- 10:00 The Use of Thrombin and Fibrinogen in Skin Grafting.  
J. MONTGOMERY DEEVER.

10:00-10:30 The Clinical Use of Anticoagulants.  
EDGAR V. ALLEN, Rochester, Minn.

10:30-11:30 Clinical Pathological Conference.  
JAMES E. PAULLIN, Atlanta, Ga.  
CLARK BROWN.

Wednesday, May 15, 1946 (continued)

H-2

## LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

## Surgical Amphitheatre

(Capacity, 100)

- 9:00- 9:15 The Diagnosis of Pericarditis.  
THOMAS C. GARRETT.
- 9:15- 9:30 A Case of Wolf-Parkinson-White Syndrome.  
DANIEL B. PIERSON, JR.
- 9:30- 9:50 Obstetrics and the Cardiac Patient.  
ROSS B. WILSON.
- 9:50-10:10 The Choice of Anesthetic for the Cardiac Patient.  
FRANCIS J. AUDIN.
- 10:10-10:30 Low Salt Diets in Cardiac Disorders.  
EARL A. DAUGHERTY.
- 10:30-11:30 Cardiac Clinic.  
PAUL D. WHITE, Boston, Mass.

J

## PENNSYLVANIA HOSPITAL

(8th and Spruce Streets)

## Auditorium

(Capacity, 100)

- 9:30-10:10 Some Clinical Applications of the Anoxia Tests.  
THOMAS W. CLARK.
- 10:10-10:50 Diagnosis and Treatment of Pericarditis.  
JOSEPH B. VANDER VEER.
- 10:50-11:30 Treatment of Cardiac Emergencies.  
L. S. CAREY.

K

## PHILADELPHIA GENERAL HOSPITAL

(34th Street below Spruce)

## Surgical Amphitheatre

(Capacity, 225)

- 9:00- 9:50 Medical Clinic.  
WILLIAM S. MIDDLETON, Madison, Wis.
- 9:50-10:40 Subacute Bacterial Endocarditis.  
CHESTER S. KEEFER, Boston, Mass.
- 10:40-11:30 Clinical Pathological Conference.  
WILLIAM B. PORTER, Richmond, Va.  
WILLIAM E. EHRLICH.

Wednesday, May 15, 1946 (continued)

L-1

**PRESBYTERIAN HOSPITAL**  
(39th Street and Powelton Avenue)

**Gymnasium**  
(Capacity, 150)

- 9:00-10:00 Diabetic Clinic.  
ELLIOTT P. JOSLIN, Boston, Mass.
- 10:00-10:30 Hemochromatosis.  
GEORGE P. ROUSE, JR.
- 10:30-11:00 Studies in Insulin Allergy.  
MERLE M. MILLER.
- 11:00-11:30 The Use of Insulin Mixtures.  
ARTHUR COLWELL, Evanston, Ill.

L-2

**PRESBYTERIAN HOSPITAL**  
(39th Street and Powelton Avenue)

**Laboratory**  
(Capacity, 10)

**DEMONSTRATIONS**

- 9:00-10:30 Methods of Laboratory Survey in Clinical Endocrinology: Demonstration of Hormone Assays.  
OLIVE HOFFMAN.
- 10:30-11:30 Demonstration of Bone Marrow Punctures.  
JOHN HOOKER AND STAFF.

M-1

**TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL**

(3400 N. Broad Street)

**Medical School Building, Room 316**  
(Capacity, 400)

Symposium on Treatment and Management of Essential Vascular Hypertension.

CHARLES L. BROWN, *Presiding*.

- 9:00- 9:30 Renal Blood Flow.  
M. J. OPPENHEIMER.
- 9:30-10:00 Experimental Hypertension.  
DEAN A. COLLINS.
- 10:00-10:30 Psychosomatic Aspects of Hypertension.  
EDWARD WEISS.  
LEON SAUL.
- 10:30-11:00 Potassium Thiocyanate Therapy.  
THOMAS M. DURANT.
- 11:00-11:30 Surgical Treatment of Hypertension.  
W. EMORY BURNETT.

Wednesday, May 15, 1946 (continued)

M-2

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

(3400 N. Broad Street)

X-Ray Museum, 6th Floor

(Capacity, 90)

JOHN LANSBURY, *Presiding*.

- 9:00- 9:30 Roentgen Demonstration of Diseases in the Small Intestine with Particular Reference to Lesions Causing Disturbed Motility.  
BARTON R. YOUNG.
- 9:30-10:30 Pitfalls in X-Ray Diagnosis.  
W. EDWARD CHAMBERLAIN.
- 10:30-11:00 Untoward Effects of Thiamine.  
GEORGE E. FARRAR, JR.
- 11:00-11:30 Evidence for Avitaminosis in Calcinosis.  
JOHN LANSBURY.

Thursday, May 16, 1946

B

GRADUATE HOSPITAL OF THE  
UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 100)

- 9:00-10:00 Diabetic Clinic.  
JOSEPH T. BEARDWOOD, JR.
- 10:00-10:30 Chemical Survey in Diabetic Acidosis.  
JOHN EIMAN.
- 10:30-11:00 Insulinomas, Benign and Malignant.  
JOSEPH T. BEARDWOOD, JR.  
JOSEPH C. YASKIN.
- 11:00-11:30 Observations on Use of Thiouracil in Thyrotoxicosis.  
JOSEPH T. BEARDWOOD, JR.  
GEORGE P. ROUSE, JR.

D-1

HOSPITAL OF THE UNIVERSITY  
OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Amphitheatre

(Capacity, 200)

- 9:30-10:00 Hepatic Disturbances in Biliary Tract Disease.  
JONATHAN C. MEAKINS, Montreal, Can.

## Thursday, May 16, 1946 (continued)

- 10:00-10:30 Laboratory Aids in the Diagnosis of Hepatic Disease.  
JOHN R. NEEFE.
- 10:30-11:00 Nutritional Factors in Hepatic Disease.  
PAUL GYORGY.
- 11:00-11:30 Problems in Hepatic Diagnosis.  
THOMAS E. MACHELLA.

## D-2

UNIVERSITY OF PENNSYLVANIA  
MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room, Medical Laboratories

(Capacity, 213)

- 9:30- 9:55 Some Basic Principles of Etiology and Treatment in Allergy.  
R. A. KERN.
- 9:55-10:20 Inter-relationships between Allergy and Other Disease of the Respiratory Tract.  
H. P. SCHENCK.
- 10:20-10:45 The Role of Allergy in Dermatologic Practice.  
N. R. INGRAHAM, JR.
- 10:45-11:30 The Significance of Allergy in the Interpretation of Disease.  
R. A. COOKE, New York, N. Y.

## E THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL

(111 N. 49th Street)

Auditorium

(Capacity, 250)

- 9:00- 9:20 The Wish to Be Ill.  
EARL D. BOND.
- 9:20- 9:40 Some Observations on Anxiety.  
OTTOMER E. RAEZER.
- 9:40-10:00 Manifestations of Emotionally Disturbed Physiology in Medical Practice.  
LOUIS H. TWYEFFORT.
- 10:00-10:20 Psychosomatic Medicine.  
HERBERT GASKILL.
- 10:20-10:40 Psychosomatic Aspects of Peptic Ulcer.  
HOWARD P. ROME.
- 10:40-11:00 The Present Status of Brain Changes in Electrical Shock Treatment.  
BERNARD J. ALPERS.
- 11:00-11:20 Treatment of Functional Conditions.  
KENNETH E. APPEL.
- 11:20-11:40 Neurological Disturbances Following Flight to High Altitudes.  
RICHARD L. MASLAND.

Thursday, May 16, 1946 (continued)

F-1

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Clinical Amphitheatre, 1st Floor

(Capacity, 300)

CLINIC

9:00- 9:40 Menopause.

ABRAHAM E. RAKOFF.

9:40-10:30 Diseases of the Thyroid.

KARL E. PASCHKIS.

10:30-10:40 INTERMISSION.

10:40-11:30 Obscure Fever.

HOBART A. REIMANN.

F-2

JEFFERSON MEDICAL COLLEGE

(1025 Walnut Street)

Society Room

(Capacity, 96)

DEMONSTRATION

9:00-11:00 Intramarrow Infusions.

LEANDRO M. TOCANTINS.

F-3

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Annex, 4th Floor

(Capacity, 18)

DEMONSTRATION

9:00-10:00 Bronchoscopy for Diagnosis.

LOUIS H. CLERF.

G

JEWISH HOSPITAL

(York and Tabor Roads)

Medical Wards

(Capacity, 20)

9:30-10:30 Ward Walk: Diagnosis and Treatment of Subacute Bacterial Endocarditis.

MITCHELL BERNSTEIN.

10:30-11:30 Carcinoma of Thymus Gland.

HAROLD GOLDBURGH.

Thursday, May 16, 1946 (continued)

H-1

**LANKENAU HOSPITAL**  
(Corinthian and Girard Avenues)

Nurses' Auditorium

(Capacity, 200)

- 9:00- 9:15 Penicillin in Peritonitis.  
ALBERT MARTIN.
- 9:15- 9:30 Penicillin Failures in Early Syphilis.  
JOHN LENTZ.
- 9:30- 9:45 Penicillin in C.N.S. Syphilis.  
CHARLES RUPP.
- 9:45-10:00 Penicillin via the Respiratory Route.  
CHARLES S. STAHLNECKER.
- 10:00-10:15 Penicillin in Asthma.  
MALCOLM W. MILLER.
- 10:15-10:30 Penicillin in Postoperative Complications.  
CHARLES JONES.
- 10:30-11:30 Clinic.  
CHESTER S. KEEFER, Boston, Mass.

H-2

**LANKENAU HOSPITAL**  
(Corinthian and Girard Avenues)

Surgical Amphitheatre

(Capacity, 100)

- 9:00- 9:20 Gastroscopic Observations.  
RENDALL R. STRAWBRIDGE.
- 9:20- 9:45 X-Ray Findings in Pyloric Obstruction.  
JOHN T. FARRELL.
- 9:45-10:15 Diagnostic Features, Carcinoma of the Stomach.  
GILSON C. ENGEL.
- 10:15-10:40 Sub-total and Total Gastrectomy, Physiological Results.  
R. GAYLE SPANN.
- 10:40-11:00 Hypoproteinemia.  
THEODORE STEVENSON.
- 11:00-11:30 Discussion.  
JOHN H. WILLARD.

J

**PENNSYLVANIA HOSPITAL**  
(8th and Spruce Streets)

Auditorium

(Capacity, 100)

- 9:30-10:00 Infectious Hepatitis.  
GARFIELD G. DUNCAN.
- 10:00-10:30 Migraine.  
PERRY MACNEAL.

Thursday, May 16, 1946 (continued)

- 10:30-11:00 Management of the Chronic Asthmatic Patient.  
J. S. McLAUGHLIN.
- 11:00-11:30 Recent Advances in Allergy.  
LEONARD PARKHURST.

**K** **PHILADELPHIA GENERAL HOSPITAL**  
(34th Street below Spruce)  
Surgical Amphitheatre  
(Capacity, 225)

- 9:00-10:40 Clinic on Gastrointestinal Diseases.  
WALTER L. PALMER, Chicago, Ill.  
RUSSELL S. BOLES.
- 10:40-11:30 Clinical Pathological Conference.  
THOMAS M. DURANT.  
WILLIAM E. EHRLICH.

**M-1** **TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL**  
(3400 N. Broad Street)  
Medical School Building, Room 316  
(Capacity, 400)

GEORGE E. FARRAR, JR., *Presiding*.

- 9:00- 9:30 Causes and Management of Diabetic Acidosis.  
WALDO E. NELSON.
- 9:30-10:00 Acute Generalized Obstructive Emphysema of Lungs in Infants.  
B. B. BARTRAM.
- 10:00-10:20 Bone Marrow Aspiration Biopsy: Selection and Interpretation.  
ELEANOR VALENTINE.
- 10:20-10:40 Relationship of Osteoporosis and Multiple Myeloma.  
ROBERT ROBBINS.  
ERNEST E. AEGERTER.
- 10:40-11:30 Recognition of the Emotional Problems Which Produce Psychosomatic  
Symptoms.  
O. SPURGEON ENGLISH.

**M-2** **TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL**  
(3400 N. Broad Street)  
X-Ray Museum, 6th Floor  
(Capacity, 90)

- 9:00-11:30 Chest Conference.  
W. EDWARD CHAMBERLAIN, *Presiding*.



**Thursday, May 16, 1946 (continued)**

Particularly interesting and unusual cases of Pulmonary Disease will be presented, including Chronic Suppurative Pulmonary Disease, Pulmonary Neoplasm, Tuberculosis, Viral Pneumonitis, Pulmonary Cyst, and others. Informal discussion is invited.

W. EDWARD CHAMBERLAIN, Roentgenology.

CHARLES L. BROWN, Internal Medicine.

W. EMORY BURNETT, Surgery.

LOUIS COHEN, Tuberculosis.

CHEVALIER L. JACKSON, Bronchoscopy.

EARLE H. SPAULDING, Bacteriology.

ERNEST E. AEGERTER, Pathology.

**O WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA**

**Philadelphia General Hospital**

**(34th Street below Spruce)**

**Nurses' Auditorium**

**(Capacity, 200)**

9:00-10:00 The Treatment of Subacute Bacterial Endocarditis.

FRANCIS G. BLAKE, New Haven, Conn.

10:00-11:30 Clinico-Pathological Conference.

WALLACE M. YATER, Washington, D. C.

JEFFERSON H. CLARK.

J. Q. GRIFFITH, JR.

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**Friday, May 17, 1946****B****GRADUATE HOSPITAL OF THE  
UNIVERSITY OF PENNSYLVANIA**

**(19th and Lombard Streets)**

**North Lecture Room**

**(Capacity, 100)**

9:00-10:50 Allergy Clinic.

MERLE M. MILLER.

R. A. COOKE, New York, N. Y.

LESLIE N. GAY, Baltimore, Md.

10:50-11:30 Clinic: Gastrointestinal Allergy.

A. F. R. ANDRESEN, Brooklyn, N. Y.

**D-1****HOSPITAL OF THE UNIVERSITY  
OF PENNSYLVANIA**

**(36th and Spruce Streets)**

**Medical Amphitheatre**

**(Capacity, 200)**

9:30-10:00 Management of Acute Coronary Occlusion.

CHARLES C. WOLFERTH.

Friday, May 17, 1946 (continued)

- 10:00-10:20 The Oximeter.  
FRANCIS C. WOOD.  
ARTHUR M. ROGERS.
- 10:20-10:40 Penicillin in Subacute Bacterial Endocarditis.  
HARRISON F. FLIPPIN.
- 10:40-11:00 Cardiac Auscultation.  
ALEXANDER MARGOLIES.
- 11:00-11:30 Management of Hypertension.  
J. Q. GRIFFITH, JR.

D-2 UNIVERSITY OF PENNSYLVANIA  
MEDICAL SCHOOL BUILDING  
(36th Street and Hamilton Walk)  
Lecture Room, Medical Laboratories  
(Capacity, 213)

- 9:30-10:00 Cardiac Resuscitation.  
ROBERT D. DRIPPS.
- 10:00-10:30 Penicillin in Neurosyphilis.  
GEORGE D. GAMMON.
- 10:30-11:00 Occupational Disease.  
LEMUEL C. MCGEE, Wilmington, Del.
- 11:00-11:30 Diabetes.  
FRANCIS D. W. LUKENS.

F-1 JEFFERSON HOSPITAL  
(10th and Sansom Streets)  
Clinical Amphitheatre, 1st Floor  
(Capacity, 300)  
CLINIC

- 9:00- 9:40 Tuberculosis.  
BURGESS L. GORDON.
- 9:40-10:30 Bronchiectasis.  
MARTIN J. SOKOLOFF.
- 10:30-10:40 INTERMISSION.
- 10:40-11:30 Bronchial Obstruction; Its Causes and Effects.  
LOUIS H. CLERF.

F-2 JEFFERSON MEDICAL COLLEGE  
(1025 Walnut Street)  
Society Room  
(Capacity, 96)

DEMONSTRATION

- 9:00-11:00 Blood Supply of Gall-bladder, Duodenum and Liver in Relation to  
Bleeding Peptic Ulcer.  
N. A. MICHELS.

Friday, May 17, 1946 (continued)

J

## PENNSYLVANIA HOSPITAL

(8th and Spruce Streets)

Auditorium

(Capacity, 100)

- 9:30-10:00 Pulmonary Disease Simulating Tuberculosis.  
E. WAYNE MARSHALL.
- 10:00-10:30 Peripheral Vascular Disturbances in the Medical Patient.  
MAURICE SACKY.
- 10:30-11:00 Pulmonary Changes in Vascular Disease.  
DAVID A. COOPER.
- 11:00-11:30 Streptomycin.  
GARFIELD G. DUNCAN.

K

## PHILADELPHIA GENERAL HOSPITAL

(34th Street below Spruce)

Surgical Amphitheatre

(Capacity, 225)

- 9:00-10:00 Rheumatic Disease.  
RICHARD H. FREYBERG, New York, N. Y.
- 10:00-11:30 Psychosomatic Clinic.  
EDWARD A. STRECKER.

M-1

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

(3400 N. Broad Street)

Medical School Building, Room 316

(Capacity, 400)

CHARLES L. BROWN, *Presiding.*

- 9:00-9:30 Roentgen Demonstration of Some Common and Unusual Lesions of the  
Upper Alimentary Tract.  
BARTON R. YOUNG.
- 9:30-10:00 Hiatal Hernia of Stomach.  
CHARLES L. BROWN.
- 10:00-10:30 Esophagoscopy and Gastroscopy.  
CHEVALIER L. JACKSON.
- 10:30-11:00 Esophago-gastric Lesions from a Surgical Viewpoint.  
W. EMORY BURNETT.
- 11:00-11:30 Diagnosis and Treatment of Cirrhosis of Liver.  
WILLIAM A. SWALM.

Friday, May 17, 1946 (continued)

M-2a

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

(3400 N. Broad Street)

X-Ray Museum, 6th Floor

(Capacity, 90)

JOHN LANSBURY, *Presiding.*

9:00-10:00 Fundal Changes in Arteriolar Hypertension. Lantern slide demonstration.

WALTER I. LILLIE.

M-2b

TEMPLE UNIVERSITY MEDICAL  
SCHOOL AND HOSPITAL

Following this there will be a demonstration of ocular fundi by use of the multilocular ophthalmoscope, in the Ophthalmology Dispensary, 2nd floor, Medical School Building. Limit 24.

10:00-10:30 Treatment of Neurosyphilis.

SHERMAN F. GILPIN.

10:30-11:00 Indications for and Interpretation of Air Encephalograms.

MICHAEL SCOTT.

11:00-11:30 Demonstration of Hydro-dynamics of the Cranio-vertebral Cavity.

W. EDWARD CHAMBERLAIN.

N

UNITED STATES NAVAL HOSPITAL

(Broad Street and Pattison Avenue)

Library Seminar Room

(Capacity, 36)

CAPTAIN WALTER H. SCHWARTZ, (MC). USN, Chairman.

9:30-10:00 Clinical Malaria and Relapse.

10:00-10:30 Peptic Ulcer in Young Service Personnel.

10:30-11:00 Amebic Liver Abscess.

11:00-11:30 Physical Medicine: Clinic and Demonstration.

Transportation will be furnished by Navy bus

(Courtesy of Captain M. J. Aston, (MC), USN, Medical  
Officer in Command, U. S. Naval Hospital)

Leave: Benjamin Franklin Hotel at 8:50 A.M.

Leave: Bellevue-Stratford Hotel at 9:00 A.M.

Return: Following the Clinics, directly to Convention Hall.

*OBITUARIES*

## DR. GILBERT THOMPSON BROWN

Dr. Gilbert Thompson Brown, Dayton, Ohio, died November 17, 1945. He was born on August 13, 1869, at West Manchester, Ohio. After attending the Manchester public schools, he matriculated at Otterbein University and was graduated four years later. He then attended the Ohio State University College of Medicine, then known as the Starling Medical College, and received his medical degree in 1895.

Dr. Brown engaged in the general practice of medicine in Dayton and served for many years as Medical Director of the Gem City Life Insurance Company. He was a member of the Montgomery County Medical Society, Ohio State Medical Association, and the American Medical Association.

His chief interest in medicine was in the treatment of tuberculosis. In the latter part of his life he gave up the active practice of medicine, but was interested in art and developed considerable skill along this line. His many friends and patients view with deep regret his passing.

A. B. BROWER, M.D., F.A.C.P.,  
Governor for Ohio

## DR. VAN NEWHALL MARSH

Dr. Van Newhall March, an Associate of the College, Painesville, Ohio, died in Ukiah, California, July 25, 1945, at the age of 69, of cerebral thrombosis.

Dr. Marsh attended the University and Bellevue Hospital Medical College, New York City, graduating in 1899. He also received a medical degree in 1900 from the Cleveland College of Physicians and Surgeons. For many years he was a member of the staff of the Lake County Memorial Hospital, and College Physician to Lake Erie College.

He had been President of the Painesville City Board of Health, Medical Examiner for the Local Draft Board, and in 1938 was a member of the House of Delegates of the American Medical Association. He was an Associate of the American College of Physicians since 1923, by virtue of former membership in the American Congress on Internal Medicine.

## DR. WILLIAM HOPTON SMITH

In the death of Dr. William Hopton Smith in Goldsboro, North Carolina on September 29, 1945, the College lost one of its oldest and most useful members. Dr. Smith was born at Goldsboro May 29, 1882. He attended North Carolina State College and the University of North Carolina. He received his M.D. Degree from the University of Pennsylvania in 1906. He later did postgraduate studies at the University of North Carolina, Univer-

sity of Pennsylvania School of Medicine, New York Postgraduate Medical School, and the Philadelphia Poly-clinic Hospital. He was a member of the staff of the Goldsboro Hospital from 1917 until his death. He served in many professional capacities. He was County Physician of Wayne County from 1917 to 1920, for six years a member of the State Board of Medical Examiners, a Vice-President of the North Carolina Medical Society, a former Secretary and President of the Wayne County Medical Society, and President of the Fourth District Medical Society. He was a diplomate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians. Possibly his most outstanding professional contribution was his initiating the program of proposed Field Training for Physicians throughout North Carolina and his being instrumental in having this program taken over by the University of North Carolina.

In 1905, Dr. Smith married Miss Mary Elizabeth Poole. Their whole life was happy and ideal. Mrs. Smith survives Dr. Smith along with two children, Miss Elizabeth Smith of Goldsboro and Lt. Wally Smith of the U.S.N.R.

Dr. Smith was an able physician and a fine citizen who took an active part in the civic life of his community. He was an Elder in the First Presbyterian Church for twenty-four years. He was among the first members of the Goldsboro Rotary Club of which organization he served as President. He was interested in and promoted Boy Scout work in Goldsboro. He was a credit to his family, his profession, and his community, and will be sorely missed by all who knew him.

PAUL F. WHITAKER, M.D., F.A.C.P.,  
Governor for North Carolina

#### DR. HOWARD SPENCER BRASTED

Howard Spencer Brasted, M.D., F.A.C.P., Hornell, New York; born, Hornell, 1888; attended the Lawrenceville School; A.B., 1910, and A.M., 1913, Hamilton College; M.D., 1914, Columbia University College of Physicians and Surgeons; postgraduate study at the New York Post-Graduate Medical School and Hospital; for many years, Visiting Physician, Pathologist and Lecturer on Materia Medica and Obstetrics, Bethesda Hospital; Examining Physician, Draft Board, New York Selective Service; past President, Hornell Medical and Surgical Association; member, Steuben County Medical Society, New York State Medical Society, and Keuka Medical Society; Fellow, American Medical Association and American College of Physicians, the latter since 1925. Death was caused by coronary thrombosis.

Dr. Brasted enjoyed a very high social and professional standing in his community. He was devoted to the practice of medicine and to his patients and will be a great loss to the profession and his family to whom our sympathy is extended.

BYRON D. BROWN, M.D.

## DR. PHILIP HALE PIERSON

Dr. Philip Hale Pierson, B.S., M.D., F.A.C.P., died in San Francisco, January 17, 1946, from cerebral thrombosis. Dr. Pierson was born on November 7, 1886, at Paoutingfu, China, where his father was a Presbyterian Missionary. After graduation from high school in Medford, Massachusetts, he entered Yale University, receiving his B.A. degree in 1908. This choice was undoubtedly influenced by the fact that an ancestor, Abraham Pierson, was the first president of Yale University. In 1913 he received an M.D. degree from Harvard Medical School, continuing his medical training in internships at the Boston City Hospital, the Clifton Springs Sanatorium, Clifton Springs, New York, and the Massachusetts General Hospital. In 1915 Dr. Pierson came to San Francisco and became associated with Dr. Philip King Brown, through which association he became a visiting physician at the Arequipa Sanitarium for women, at Manor, Marin County, California. This appears to have stimulated his beginning interest in diseases of the chest. In 1916, joining the staff of Stanford University Medical School in San Francisco he rose steadily in rank, becoming Clinical Professor of Medicine in 1933. Other clinical appointments were: Chief of the Department of Tuberculosis, Stanford University and San Francisco Hospitals; consultant in diseases of the chest, Community Hospital, San Mateo County, Veterans' Administration Facility, and Hassler Health Home (Redwood City). The following list of medical society memberships and allied activities indicates Dr. Pierson's range of interests and his prominence in the field of tuberculosis: California Academy of Medicine; San Francisco County and California State Medical Societies; Fellow of the American Medical Association and the American College of Physicians (1930); member, National Association of Tuberculosis; and member, Board of Directors of this Association; former President, California Tuberculosis Association; also Laennec Society. He was a member and trustee of the Calvary Presbyterian Church.

As a medical author, his contributions were largely in the domain of experimental and clinical tuberculosis, including chapters in books and systems of medicine.

Dr. Pierson is survived by his wife, Grace F. Pierson; a son, Dr. Robert E. Pierson; two daughters, Mrs. Randolph M. Forbes, and Mrs. William L. Bush.

Dr. Pierson possessed a dignified and somewhat retiring personality, but to those medical confreres who knew him well over a long period of years, he was a sincere, loyal friend. To his patients, he was a sympathetic friend as well as a capable medical consultant.

ERNEST H. FALCONER, M.D., F.A.C.P.,  
Governor for Northern California

## DR. ROBERT WARD LAMSON

Robert Ward Lamson, M.D., F.A.C.P., Los Angeles, California, died January 6, 1946, of atypical pneumonia.

Dr. Lamson was born in Amherst, Massachusetts, July 22, 1889. He received a B.S. degree in 1912, Massachusetts Agricultural College; M.A., 1917, Columbia University; Ph.D., 1922, Harvard University; M.D., 1925, Harvard Medical School; Postgraduate study at Columbia University and Harvard University. He served during his early career on the faculty of the Massachusetts Agricultural College, the Maryland Agricultural College and Harvard Medical School. He was Instructor in Bacteriology and Immunology in 1923-1924, Harvard Medical School. He was Associate Professor of Bacteriology and Immunology, 1925-1926, Baylor University Medical School. He also served as Associate Professor of Preventive Medicine and Hygiene at Baylor University in 1926 and as Associate Professor of Bacteriology and Immunology in the Baylor University Dental School at the same time. In 1929 he moved to Southern California and became Associate Professor of Bacteriology and Immunology at the University of Southern California Medical School, later being promoted to Professor of Medicine (Public Health). He was a member of the staff of the Hospital of the Good Samaritan, the Los Angeles County General Hospital, Santa Fe Hospital, and in charge of the Allergy Clinic, Eye and Ear Hospital and Olive View Sanatorium.

Dr. Lamson served as an officer in the Laboratory Service of the U. S. Army, 1917 to 1919, part of which time was served in France. He was a member of the Los Angeles County Medical Society, the California State Medical Association, the American Medical Association, the Society of Experimental Biology and Medicine and also the American Association of Immunologists. He was a Diplomate of the American Board of Internal Medicine and the author of numerous papers appearing in leading medical journals. He had been a Fellow of the American College of Physicians since 1931.

In the death of Dr. Lamson, Southern California has lost one of her most distinguished physicians and scientists.

ROY E. THOMAS, M.D., F.A.C.P.,  
Governor for Southern California

## DR. GEORGE MANNHEIMER

George Mannheimer, M.D., F.A.C.P., of New York City, died December 10, 1945. He was born in Bavaria in 1867; M.D., 1890, University of Strassburg, Germany. Soon thereafter he came to America and became attached to the Mount Sinai, Lebanon and Seaview Hospitals and the Bedford Sanatorium in the New York area. For many years he was Consulting Physician to the New York Infirmary for Women and Children. He was a



member of the New York County Medical Society, Medical Society of the State of New York, American Medical Association and the New York Pathological Society. He was a former president of the Metropolitan Medical Society and a Fellow of the New York Academy of Medicine. He was the author of numerous published papers.

Dr. Mannheimer was a Charter Fellow of the American College of Physicians having been elected in the early part of 1916.

### DR. LARUE D. CARTER

Dr. Larue D. Carter, nationally known neuropsychiatrist, died at his home in Indianapolis on January 22, 1946, after an illness of several weeks. He was sixty-five years old.

Dr. Carter was professor of neurology at the Indiana University School of Medicine, chief of the neuropsychiatric staff of the Indianapolis City Hospital, lecturer to the schools of nursing at City, Methodist and St. Vincent's Hospitals, and a member of the staff societies of Methodist and St. Vincent's Hospitals.

A native of Westfield, Indiana, and a birthright Quaker, Dr. Carter was born March 17, 1880. He was graduated from the old Medical College of Indiana in 1904 and served his internship at the City Hospital and at Philadelphia General Hospital. He also was resident physician at the Eastern Indiana Hospital at Richmond, Indiana, several years. He did postgraduate study in New York and Baltimore, and entered the Army in 1916, reaching the rank of colonel. He also acted as medical liaison officer for Indiana for the Fifth Service Command during World War II. He was a charter member of the American Legion and of Paul Coble Post of the Legion. Consultant in neuropsychiatry for Veterans' Hospital and chief consultant for the Norway Sanitarium. Dr. Carter also was Chairman of Governor Ralph F. Gates' committee for selecting the site of the new Indiana University Mental Hospital and for arranging for the hospital. He was past president of the Indianapolis Neuropsychiatric Association and of the Marion County Medical Society, and was a member of the American Medical Association, Central Neuropsychiatric Association, Association of Military Surgeons and Phi Chi Medical Fraternity. Dr. Carter had been a Fellow of the American College of Physicians since 1929, and a diplomate of the American Board of Psychiatry and Neurology.

It is with deep regret that we record the passing of Dr. Carter. The Medical Profession of Indiana has suffered a great loss.

ROBERT M. MOORE, M.D., F.A.C.P.,  
Governor for Indiana

### DR. PAUL M. GLENN

Paul M. Glenn, M.D., Associate of the American College of Physicians, was born in Cleveland, Ohio, July 9, 1906. After graduating from Ohio

State University, he attended the Medical School of Western Reserve University, Cleveland, Ohio, graduating in 1935. His internship was served in the University Hospitals of Cleveland following which he spent a year as Fellow in the Department of Gastro-enterology at the University of Pennsylvania Hospital, Philadelphia. The next two years were spent as Teaching Fellow in Medicine at his Alma Mater, and in 1940 he was appointed Instructor in Medicine and advanced to Senior Instructor in June, 1941.

On the outbreak of war, he went overseas as a Captain with the Fourth General Hospital which was sponsored by Western Reserve University. After a year's service overseas, he was forced to return because of poor health, and was assigned to the Finney General Hospital where he served as the Chief of the Gastro-enterology Service and as Assistant Chief of the Medical Service. He was promoted to the rank of Major in 1944.

Dr. Glenn was certified by the American Board of Internal Medicine. He was an Associate of the American College of Physicians, a member of the American Gastro-enterological Association, and a member of the American Federation for Clinical Research. He had contributed a number of papers on gastrointestinal diseases to the literature. He was a stimulating teacher, a competent investigator, and had a lovable personality.

Dr. Glenn died at the Lawson General Hospital, Atlanta, Ga., on December 21, 1945, of disseminated lupus erythematosus. His death has deprived the profession of an unusually competent and promising young internist. He is survived by his wife, Hortense Glenn, and two children, Joan Marie and Paul Mitchell, Jr.

JOSEPH M. HAYMAN, JR., M.D., F.A.C.P.,  
Cleveland, Ohio

#### DR. FRED ERNEST ANGLE

Fred Ernest Angle, B.S., M.D., F.A.C.P., Kansas City, Kansas, died October 29, 1945, of cardiovascular disease in the University of Kansas Hospital.

Dr. Angle was born in Wyandotte County, Kansas, March 1, 1900. He received his B.S. degree in 1922 from the University of Kansas, and his Medical Degree in 1926 from the School of Medicine of that institution. He was a Rotating Intern and Medical Resident at the United States Naval Hospital, Brooklyn, from 1926 to 1928; he did postgraduate study during 1930 at the New York Postgraduate Medical School. For many years he was Instructor in Medicine at the University of Kansas School of Medicine and Director of the Clinical-Pathological Laboratory at the Bethany Hospital. More recently he was Attending Physician at the Providence, Bethany and St. Margaret's Hospitals.

Dr. Angle was a member of the Wyandotte County Medical Society, Kansas State Medical Society, Kansas City Academy of Medicine, American Heart Association, Kansas City Southwest Clinical Society, and the Ameri-

can Medical Association. He had been a Fellow of the American College of Physicians since 1938. He was the author of numerous published papers. He did pioneer work in the cause, distribution and treatment of undulant fever. He also made extensive investigations into agranulocytic angina.

HAROLD H. JONES, M.D., F.A.C.P.,

Governor for Kansas

### DR. FREDERICK LANE BROWN

Death has taken from this community a beloved friend, counsellor and prominent physician. Dr. Frederick Lane Brown, F.A.C.P., died on January 30, 1946, at the Neurological Institute in New York from a brain tumor. He had become ill on December 18, 1945, while on a professional visit.

Dr. Brown was born in Somerville, New Jersey, on January 13, 1883. He was graduated from Princeton University in 1905. He then entered the employ of the American Locomotive Company, but soon decided on a medical career, and in 1910 was graduated from the College of Physicians and Surgeons of Columbia University. Following two years of internship, he opened his office in New Brunswick, where he remained for his lifetime.

In his early years, Dr. Brown was interested chiefly in obstetrics and pediatrics. Although he later specialized in internal medicine, he retained his love for children and always enjoyed ministering to their needs.

Dr. Brown was a member and, in 1930, President of the Middlesex County Medical Society. He was elected a member of the Executive Council for 1946. He was for many years chief of medicine at the Middlesex General Hospital and a staff member at St. Peter's General Hospital. During the War, he was chairman of the Committee for the Procurement and Assignment of Physicians. He also served as a member of Advisory Board No. 10 to the Selective Service and his advice was a matter of gratification to those who served with him. He was a Fellow of the American College of Physicians since 1926. Among all his organizations, the College membership was his pride and the one that gave him the greatest satisfaction and pleasure. We often spent evenings together, discussing College problems and devising plans for the improvement of the local College membership.

Dr. Brown was a deeply and genuinely religious man. To the day of his death he served as an elder of the Reformed Church. His spare hours he spent in a cottage in the Watchung Mountains or in assorting and cataloguing his collection of book plates.

Above all, however, Dr. Brown was a loyal friend, not only to his intimates, but to the medical fraternity. He encouraged the younger men toward progress and achievement. No amount of work would prevent him from giving counsel to a young physician. Never did an institution call on him in vain for his advice and for the benefit of his mature judgment.

His death came as a shock to his widow and his two children, but the entire community joins them in their grief at the loss of a real friend.

KARL ROTHSCHILD, M.D., F.A.C.P.

# ANNALS OF INTERNAL MEDICINE

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## MENINGOCOCCIC INFECTIONS IN AN ARMY STAGING AREA: ANALYSIS OF 63 CASES WITHOUT FATALITY FROM THE STANDPOINT OF EARLY DIAG- NOSIS AND TREATMENT\*

By A. ALLEN GOLDBLOOM, Lt. Col., M.C., A.U.S., F.A.C.P., EMANUEL H.  
NICKMAN, Major, M.C., A.U.S., and EDWARD E. P. SEIDMON, Major,  
M.C., A.U.S., *New Brunswick, N. J.*

WITHIN recent years medical opinion with regard to meningococcal infections and their treatment has undergone drastic revision. The early twentieth century concept that the meningococcus invades the meninges by way of the nasopharynx and cribriform plate was challenged in 1918 by Herrick<sup>1</sup> and later by others.<sup>2,3,4</sup> They expressed the belief that the infection enters the body through the nose and throat and then spreads to the blood stream which carries it to the various body tissues including the meninges where it becomes localized. However, if the resistance of the host is sufficiently great or if therapy is early and effective, the invasive process may be halted in the nasopharynx or in the blood stream and meningitis will not ensue. Therapy also has undergone a metamorphosis. Since the advent of the sulfonamides indications for the use of antimeningococcus serum and meningococcus antitoxin have gradually become more restricted because of the efficiency of chemotherapeutic agents in lowering mortality rates and decreasing the frequency of sequelae.

Two major problems, however, have not yet been completely solved, namely: (1) early diagnosis prior to localization of the organism in the meninges, especially in sporadic cases, and (2) optimum sulfonamide dosage. We have attempted in this paper to present findings which may be of assistance in the partial solution of these problems as well as to present an analysis of 63 cases of meningococcal infections treated at this institution.

\* Received for publication Sept. 26, 1945.

From the Medical Service, Station Hospital, Camp Kilmer, New Jersey.

## EPIDEMIOLOGY AND VITAL STATISTICS

Medical statistics and literature have noted the increased incidence of meningococcal infections during wars when individuals are brought together for the first time in large groups. In World War I, 5839 cases were reported<sup>5</sup> among military personnel between April 1, 1917 and December 31, 1919.

The infection "was of relatively low incidence and was sporadic rather than epidemic in its occurrence in the Army, but its extremely high mortality made it of great importance as a cause of death in the United States forces. The case fatality varied in different camps from 9 to 63 per cent." "There were 2279 deaths, a mortality of 39 per cent." During the years following World War I the incidence declined but again rose in 1943. In that year an increased number of cases was reported, especially among troops. The mortality, however, was much lower than in the First World War owing to the use of sulfonamides. Recent mortality estimates have varied between 3 per cent and 10 per cent.

In the period between July 4, 1942 and July 4, 1945, 63 cases of meningococcal infections were treated in the Station Hospital, Camp Kilmer, New Jersey. Sulfadiazine and its sodium salt were the sole therapeutic agents. No fatalities occurred in this consecutive series of cases. All patients recovered and were returned to duty. Within the period mentioned above slightly over one million seasoned troops were quartered and processed in this Camp preparatory to overseas movement. Transient troops made up over two-thirds of the cases seen. Not more than one case occurred in any one organization. The same was true of the small group of cases among permanent personnel of the Post. One case was seen in a white child, five years of age, the daughter of a soldier not stationed in this Camp. All cases were separated by a sufficiently wide interval of time to indicate that they were sporadic in character. Despite the fact that no epidemic per se existed on this Post, a greater number of cases was seen during 1942 and 1943 when a higher incidence of meningococcal infections existed among military personnel in the United States.

Racial distribution of cases included 54 (85.7 per cent) white patients and nine (14.3 per cent) colored patients.

Thirty-eight (60.3 per cent) patients came from urban and 25 (39.7 per cent) from rural communities and from these figures no conclusions can be drawn as to the significance of environment upon the incidence of meningococcal infections. Thomas<sup>7</sup> makes a similar observation.

Ages ranged from five to 54 years, the average being 26.6 years. The maximum number of cases (38) occurred in the age group of 20 to 30 years (60.3 per cent).<sup>3, 8</sup>

Nearly all of our patients (95.2 per cent) were seasoned soldiers with a minimum army service of five months and a maximum of nine years; 70.8 per cent fell into the service group of five months to one year and three

months. Only 4.8 per cent of soldiers had less than five months service. This incidence is in contrast to that found by Denny, Bausch and Turner<sup>3</sup> who reported that 82 per cent of their cases occurred in raw recruits with an average service of 2.7 months, and to that of Thomas<sup>7</sup> who noted that two-thirds of cases occurred in soldiers of less than three months service.

### CLINICAL CONSIDERATIONS

From a study of the literature the erroneous impression is created that the diagnosis of meningococcal infections is comparatively clear-cut with a definite train of symptoms and signs which invariably include petechiae, stiff neck, Kernig's and various other neurological signs. This is true in epidemic periods when the course of the disease is so rapid and the nasopharyngeal and bacteremic stages are so evanescent that only the picture of a typical meningitis is present when the patient is first seen by the physician. However, in sporadic or chronic cases the above mentioned findings are not always present on admission and if present are frequently overshadowed by signs and symptoms referable to the skin, nasopharynx, blood stream, musculo-skeletal system and gastrointestinal tract. In over 50 per cent of our cases signs and symptoms of meningitis were absent on admission and findings suspicious of the following conditions were present: common respiratory infections, rheumatic fever, arthritis, appendicitis, acute exanthemata, obscure dermatological conditions, erythema multiforme, erythema nodosum, subacute bacterial endocarditis, undulant fever, psychosis, hysteria and acute alcoholic intoxication.

Early differential diagnosis is made the more difficult in sporadic cases because the percentage of positive blood cultures, the percentage of rash, the clarity of the symptomatology and the awareness of the physician of the possibility of meningococcal infection are less than in epidemics.

The function of our camp being the handling of large bodies of constantly moving troops, it may be seen that early and rapid diagnosis was of great importance to us, not only from the standpoint of the cure of the patient, but also for the purpose of treating contacts and carriers prophylactically to prevent them from acting as foci for the spread of the infection aboard crowded transports.

Accordingly, in order to facilitate early diagnosis and to better evaluate the relative importance of the signs and symptoms in meningococcal infections, we tabulated them as "early," occurring before or on admission to the hospital and "late," occurring subsequent to admission. The principal early findings in order of frequency were: nasopharyngitis, fever, headache, malaise, vomiting, myalgia and arthralgia and nuchal tenderness, splinting or rigidity. Of lesser frequency were: petechiae, nausea, irrationality, Kernig's sign, apathy or semi-coma, backache, coma, Brudzinski's sign and diaphoresis. A study of figure 1 makes evident the fact that the so-called classical findings do not necessarily occur early, but may develop later in the

disease and are of no help in establishing an early diagnosis. In our series no patient gave a history of contact and over 50 per cent were admitted to the hospital for conditions other than meningococcal infections, subsequent observation and study establishing the correct diagnosis. It is obvious from an analysis of figure 1 that, despite our desire to find significant early criteria, the early findings are not diagnostic of meningococcal infection but are common to a number of disease syndromes. However, it must be emphasized that in spite of their lack of specificity the frequency of their occurrence makes it imperative that one always consider meningococcal infection in the differential diagnosis when these findings are present.

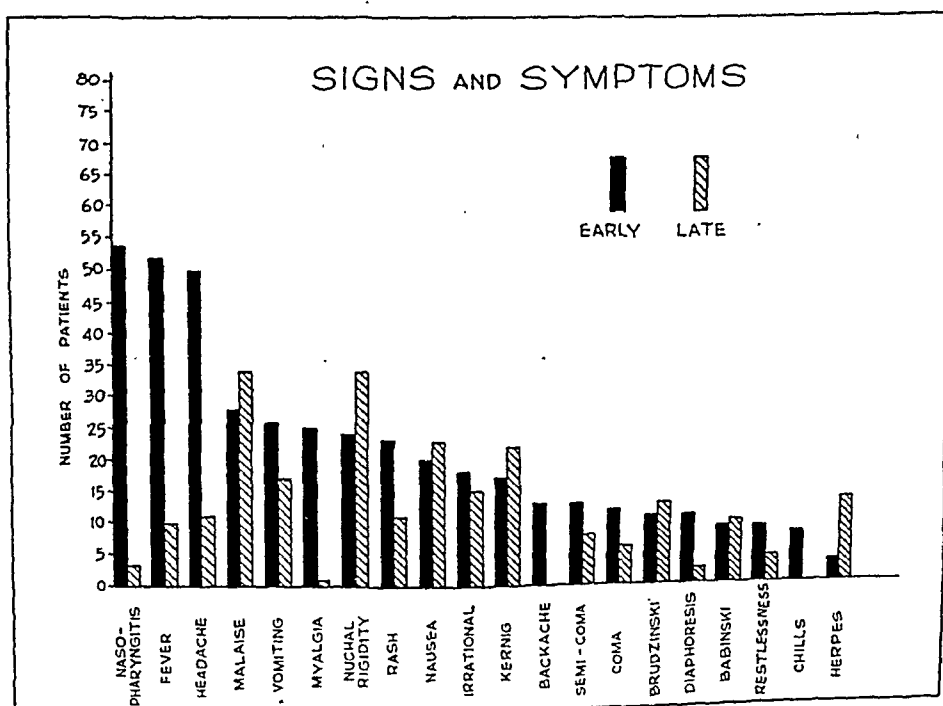


FIG. 1. Comparative frequency of early and late signs and symptoms in meningococcal infections.

Temperature, pulse and respirations were significant only insofar as they indicated the presence of an acute disease process. Temperatures averaged  $102.4^{\circ}$  F. with a maximum range of  $98.6^{\circ}$  to  $105.2^{\circ}$  F. Fever varied in type; in some it was septic and in others sustained low grade. The average pulse rate was 106.4 beats per minute, the highest recorded being 130 and the lowest 60. Respirations averaged 25.1 per minute. The highest rate was 40 and the lowest 16.

In this series we have classified our cases as mild (+), average (++), severe (+++) and fulminating (++++) depending upon the severity of the signs and symptoms, the rapidity of onset and the course of the disease. Eleven cases (17.5 per cent) were mild, 23 (36.5 per cent) were average, 23 (36.5 per cent) were severe and six (9.5 per cent) were fulminating or

moribund. The following typical case histories are illustrative of the above classified types:

1. Case history illustrative of the mild type of meningococcal infection:

A private first class was admitted to the hospital with a diagnosis of nasopharyngitis, having had cough, sore throat and mild headache for 24 hours. Upon admission he said that he did not feel ill except for a moderate generalized headache. Physical examination revealed a well nourished white male, 19 years of age, who did not appear to be very sick despite a temperature of 103.8°. No cutaneous rashes were present. His nasopharyngeal mucosa was red and edematous. Nuchal tenderness was present but forward motion of the head was only slightly impaired. The spinal fluid was cloudy, under moderate pressure and contained 4150 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. The spinal fluid sugar was 57.5 mg. per cent and the spinal fluid total protein was 100 mg. per cent. Culture of the fluid was positive for type I meningococcus. The blood culture showed no growth. Response to sulfadiazine therapy was prompt and uninterrupted, the patient becoming temperature-free on the third hospital day and symptom-free on the sixth hospital day. A total dosage of 52.5 grams of sulfadiazine was used. No complications or sequelae were encountered and the patient was discharged fully recovered after 44 days of hospitalization.

2. Case history illustrative of the average type of meningococcal infection:

A private first class, white male, age 40, was admitted with the complaints of mild sore throat, cough, nasal discharge, gradually increasing headache, weakness, chills, fever, somnolence, ringing in the ears and blurring of vision of three days' duration. Physical examination revealed an acutely ill soldier in a semi-stuporous state. No petechiae or other rashes were present. His throat was markedly reddened, his tongue furred and his breath fetid. Nuchal rigidity was severe, deep reflexes were hyperactive, and lateral nystagmus, Kernig's sign and ankle clonus were present. His spinal fluid was cloudy and under moderate pressure. Laboratory study gave the following information: spinal fluid—12,100 cells, 95 per cent polymorphonuclear leukocytes, total protein 750 mg. per cent, sugar 27.5 mg. per cent, culture positive for type I meningococcus; blood culture positive for meningococcus. Somnolence, nuchal rigidity, headache and hyperactive reflexes continued to be present for three days, but gradually decreased in severity under sulfadiazine therapy. On the fifth day his temperature was normal and on the sixth he was symptom free; however, he complained of weakness until the twenty-second day of hospitalization. The total sulfadiazine dosage was 48 grams. No complications or sequelae occurred. He returned to duty 46 days after admission to the hospital.

3. Case history illustrative of the severe type of meningococcal infection:

A second lieutenant, white male, age 26, was admitted in coma. A history subsequently obtained from him revealed that he had had a severe persistent headache and malaise for three days prior to hospitalization. On the day before admission he became very sleepy and developed pains in his neck, back and thighs. He apparently lost consciousness shortly thereafter as he remembered nothing of the period immediately preceding his entrance into the hospital nor for several days thereafter. The initial examination showed a well nourished white male, delirious and thrashing about in bed. His temperature was 102.6° F. Innumerable purpuric lesions varying from 0.2 to 2.5 centimeters in diameter were present upon the face, trunk and extremities. Several were noted upon the scrotum, conjunctivae and oral mucosa. The pharynx was moderately reddened. Neurological findings included: pronounced



nuchal rigidity, positive Kernig's sign, ankle clonus, lateral nystagmus and hypertonic tendon reflexes. The blood leukocyte count was 27,400 per cubic millimeter with 83 per cent polymorphonuclear cells. The spinal fluid was cloudy, under pressure and contained 15,100 white blood cells per cubic millimeter, 95 per cent of which were polymorphonuclear leukocytes. Spinal fluid showed a markedly elevated total protein, 800 mg. per cent, and moderately decreased sugar, 25 mg. per cent. The spinal fluid smear and culture as well as the blood culture demonstrated growth of gram negative diplococci which were identified as *Neisseria intracellularis*. For 24 hours the patient was wildly delirious and required physical restraint. There was some improvement on the following day, with partial return of consciousness and diminution of nuchal rigidity and rash; however, urinary incontinence, strabismus, lateral nystagmus and photophobia were still present. Consciousness was fully regained upon the third day but fever continued until the eighth day. Neurological signs consisting of weakness, areas of anesthesia and paresthesia of the lower extremities and slight pain in the left knee persisted until the seventeenth hospital day. After 57 days he was discharged to duty fully recovered. There were no sequelae.

#### 4. Case history illustrative of the fulminating type of meningococcal infection:

A private, white, 20 years of age, was admitted with a diagnosis of nasopharyngitis. He had been ill for 12 hours with cough and nasal discharge. Immediately after admission he complained of severe headache and vomited. While his admission history was being taken he lapsed into coma and appeared to be in shock. His pulse rate was 118 per minute and his blood pressure 130 mm. Hg systolic and 80 mm. diastolic. No nuchal rigidity was present and Kernig's sign was equivocal. Petechiae were noted on the abdomen and back. Two hours later the patient became maniacal and had to be restrained. His skin was cold and bathed in a profuse sweat. Petechiae had increased in number and were visible all over the body. Nuchal rigidity was present; pupils were widely dilated and did not react to light; pulse was 126 per minute and of fair volume; blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. The blood leukocyte count was 15,100, of which 97 per cent were polymorphonuclear leukocytes. The spinal fluid was cloudy, under pressure and contained 3,550 white blood cells, all of which were polymorphonuclear leukocytes. A spinal fluid smear showed the presence of intracellular diplococci. Growth of *Neisseria intracellularis* was subsequently demonstrated in the spinal fluid and blood cultures. A continuous intravenous infusion of salt solution in addition to sulfadiazine therapy was administered over a period of three days to which the patient responded slowly but progressively with gradual diminution of coma, shock and mania. Incontinence of urine and feces which was present during this period stopped on the third day. Temperature, pulse, respirations and blood pressure were normal on the fourth day. Although the patient's sensorium was not completely clear he was aware of time and place on the fifth day. Thereafter, recovery was rapid with abatement of all physical signs, nor had he any complaints except for occasional headaches, drowsiness and muscle soreness which were absent after the eighth day. He was discharged to duty on the forty-third day fully recovered.

#### LABORATORY DATA

Blood counts were usually indicative of an active infection. Most of the total white blood cell counts, 46 (73.0 per cent), fell between 10,000 and 25,000, the average being 16,030, the high 35,500 and the low 5,500. Although most of the counts showed a moderate leukocytosis, 11 (17.5 per

cent) were normal. It is important in the latter connection to keep the possibility of meningococcal infections in mind as normal or low white blood cell counts by no means exclude the diagnosis. Differential white blood cell counts invariably showed a relative leukocytosis. Polymorphonuclear leukocytes averaged 85.1 per cent, with a high of 99 per cent and a low of 63 per cent.

*Neisseria intracellularis* (meningococcus) was isolated in pure culture from the blood in 19 patients (30.2 per cent), from culture of the spinal fluid in 48 patients (76.2 per cent) and in stained spinal fluid smears in 24 patients (38.1 per cent). The type of meningococcus found was invariably type I.<sup>9</sup> In 11 cases no organism could be recovered. Of these 11 patients eight gave a history of having had sulfonamides prior to admission. Many reports have appeared in the medical literature to substantiate the fact that even small quantities of sulfonamides are sufficient to inhibit the growth of the meningococcus in spinal fluid as well as in vitro.<sup>10, 11, 12</sup> It is quite possible that such was the case in the above group. Three patients had not had sulfonamides as far as could be determined. In spite of negative cultures all of the 11 patients mentioned above had definite signs and symptoms of meningitis as well as large numbers of pus cells in their spinal fluids. The severity of these cases was: three ++++, seven ++, and one +.

The average spinal fluid cell count, exclusive of seven cases of meningococcemia described below, was 9,915. The highest count obtained was 38,400 and the lowest was 50. The degree of clarity of the spinal fluid was roughly in proportion to the cell count, those with extremely high counts being purulent, those with moderate counts being cloudy and those with low counts being clear. The cells found in the differential cell count of the spinal fluid were predominantly polymorphonuclear leukocytes.

Spinal fluid in most cases revealed a moderate to marked depression of the sugar content, and the total protein content showed a moderate increase.

#### MENINGOCOCCEMIA

Seven cases of meningococcemia are included in this presentation. The clinical findings in these patients were at some variance with those of classical meningococcic meningitis. Positive cultures were obtained in 11 additional cases, but these, when first seen, had advanced beyond the septicemic phase and presented the picture of a typical meningitis and hence are not included as meningococcemias.

Meningococcemia may be extremely protean in its manifestations. The acute form, which is the type most commonly seen in epidemics, is of rapid onset with a spiking temperature curve, high pulse and respiratory rate, moderate to marked leukocytosis, profuse generalized petechial or purpuric rash and diaphoresis. In inter-epidemic periods this type occurs less frequently or may be subacute with similar symptoms but with a more gradual onset, more prolonged course and milder clinical manifestations. The chronic and chronic recurrent types are much more difficult to diagnose.

Their onset is slow and insidious with low grade persistent or undulant types of fever curve, malaise, vague aches and pains in the muscles and joints, swelling of the joints, a relatively small number of erythematous, purpuric or nodular skin lesions, and little or no elevation of the polymorphonuclear leukocytes of the blood. This picture may persist from several days to several months. It may clear spontaneously without treatment or may eventuate in meningitis.

One of our cases had acute meningococcemia with sudden onset 24 hours before admission, innumerable petechiae, nasopharyngeal engorgement, no neurological findings and normal spinal fluid. A second case, a white child five years of age, was ill for 12 hours before admission. She had sore throat, malaise, earache, stiff knees, nausea, vomiting, nuchal tenderness and a moderate number of petechiae. The spinal fluid was crystal clear and contained five cells. The spinal fluid revealed a reduction of the sugar to 5 mg. per cent and a normal protein content. Spinal fluid smear and culture were positive for meningococcus, type I. The blood culture was positive. This case represents an acute meningococcemia and an associated extremely early invasion of the meninges from the blood stream. There were three cases of chronic meningococcemia with ill defined symptoms varying in duration from four to 27 days. They showed evidence of upper respiratory infection, had tender or swollen joints, an erythematous or purpuric rash with from five to 10 lesions present, vague aches and pains, and tender nodules in the skin of the wrists, arms and neck. Two patients, ill for 10 days and 14 days respectively before hospitalization, were found to have chronic meningococcemia with signs and symptoms as in the above group, but eventually developing meningitis.

In addition to blood culture all cases in this group, as well as others suspected of having meningococcemia, were subjected to a diagnostic spinal puncture even in the absence of meningeal signs. This procedure enabled us to make a diagnosis by the isolation of the meningococcus in the stained spinal fluid smears of four patients who had no evidence of meningeal involvement many hours before the laboratory was able to report upon the blood cultures. In view of the above findings it is apparent that the organism is capable of early penetration of the meningeal barrier and may be identified in stained spinal fluid smears before the development of clinical reactions referable to the central nervous system and before marked alterations in the spinal fluid cell count and chemistry take place. We do not wish to infer that such findings are common. They are not. Nor do we believe that, in the absence of a positive spinal fluid smear and while waiting for the blood culture report, treatment should be delayed. In the presence of clinical signs of meningococcemia vigorous and early treatment must be instituted. In doubtful cases of meningococcemia, however, examination of spinal fluid smears, even in the absence of meningeal signs, may prove to be a more rapid means of identification of the organism than blood culture with the consequent saving of many hours before treatment is begun.

## THERAPY

Immediately following the diagnosis of a meningococcic infection it is our practice to administer the sodium salt of sulfadiazine intravenously to all patients even though they may be able to take the drug by mouth. In this manner we are able to obtain a high concentration of the drug in the blood stream more rapidly than would be secured by oral administration alone. In addition to the fact that intravenous is more rapid in its effect than oral medication, the former type of therapy is doubly important because of variability in the degree and rate of absorption of sulfonamide compounds from the gastrointestinal tract.<sup>8, 13</sup> It is a grave error to underestimate the seriousness of apparently mild meningococcal infections. All patients suffering from such infections are potentially seriously ill, not only from the standpoint of mortality but also because of resulting complications and sequelae.<sup>8, 13</sup> It is important, therefore, to obtain the optimum therapeutic level of the drug at the earliest possible moment regardless of the clinical appearance of the patient.

The standard therapeutic procedure for all cases of meningococcal infections as used on our service is as follows:

1. When a diagnosis of meningococcal infection is established, or in the presence of a suspicious spinal fluid prior to laboratory confirmation of the disease, the patient is given 0.5 per cent solution (5.0 gm.) of sodium sulfadiazine in 1000 c.c. of 5 per cent glucose in saline intravenously.

2. If the patient continues to remain in coma after the initial medication he is given 0.25 per cent solution (2.5 gm.) every six hours until he is able to take the drug by mouth.

3. As soon as oral medication is possible two grams of sulfadiazine are given by mouth every four hours for the remainder of the first 24 hour period following admission, then one gram every four hours until the temperature is normal. This is followed by a dosage of one gram three times daily until all acute symptoms disappear and for two additional days thereafter.

4. Sodium bicarbonate in the amount of 10 grains for every gram of sulfadiazine is given.<sup>14</sup>

5. Body fluid levels are maintained by the daily oral or intravenous administration of 3000 to 4000 c.c. of fluid. This amount insures a urinary output of at least 1200 c.c., sufficient to minimize the frequency of sulfacrySTALLURIA.

The average total dosage of sulfadiazine per patient was 54.7 grams; the lowest was 27.0 grams and the highest 115 grams (see figure 2).

The average total oral sulfadiazine per patient was 48.0 grams; the lowest 17.0 grams and the highest 111.0 grams.

Fifty-four patients received sodium sulfadiazine intravenously, the average total dose being 7.2 grams. The lowest total dose was 4.0 grams and the highest 22.5.

Eleven patients were given sulfadiazine by gavage in an average total dose of 7.3 grams. The lowest total dose in this group was 4.0 grams while the highest was 23.0 grams. This mode of therapy was used only during a short period in 1942 and 1943. Its use thereafter was discontinued in favor of the more rapidly effective intravenous sodium sulfadiazine.

The medication given to the only child in our series is listed separately as her dosage and that of the adults are not comparable. She received 10.5 grams of sodium sulfadiazine intravenously and 11.5 grams of sulfadiazine orally, making a total dosage of 22.0 grams.

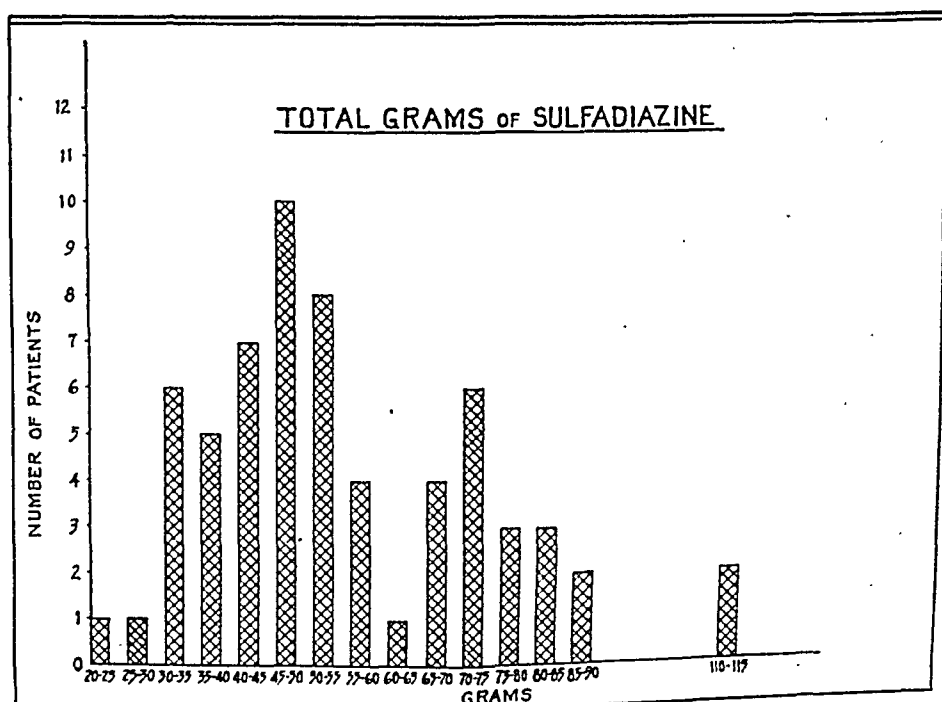


FIG. 2. Distribution of total sulfadiazine dosage in 63 patients treated for meningococcal infections.

Chemotherapy was administered to each patient for an average of 4.4 days before the temperature became normal. The longest recorded elevation was 12 days and the shortest was one day (see figure 3).

Medication was discontinued only when all signs and symptoms referable to the nervous system had subsided (see figure 3). We found it unnecessary to make cultures and sugar determinations of the spinal fluid before stopping treatment.<sup>15</sup> The clinical condition of the patient was a sufficiently reliable guide to make these procedures superfluous. No recrudescences occurred.

Patients became completely symptom-free after an average of 6.2 days. The high was 14 days and the low was three days.

Total days of chemotherapy were: average 7.6 days, high 14 days, low 3 days.

In no instance was other specific medication such as serum, antitoxin or penicillin used. Sulfadiazine and its sodium salt were the sole therapeutic agents. Supportive measures included paraldehyde for convulsive and violent patients, barbiturates for restlessness and caffeine sodium benzoate, which was helpful in some cases in reducing the severity of headaches. Opiates were not used.

We were unable to obtain figures for sulfadiazine blood levels which appeared to have any correlation with the therapeutic results obtained. In many cases where patients were receiving the same amount of drug the sulfa

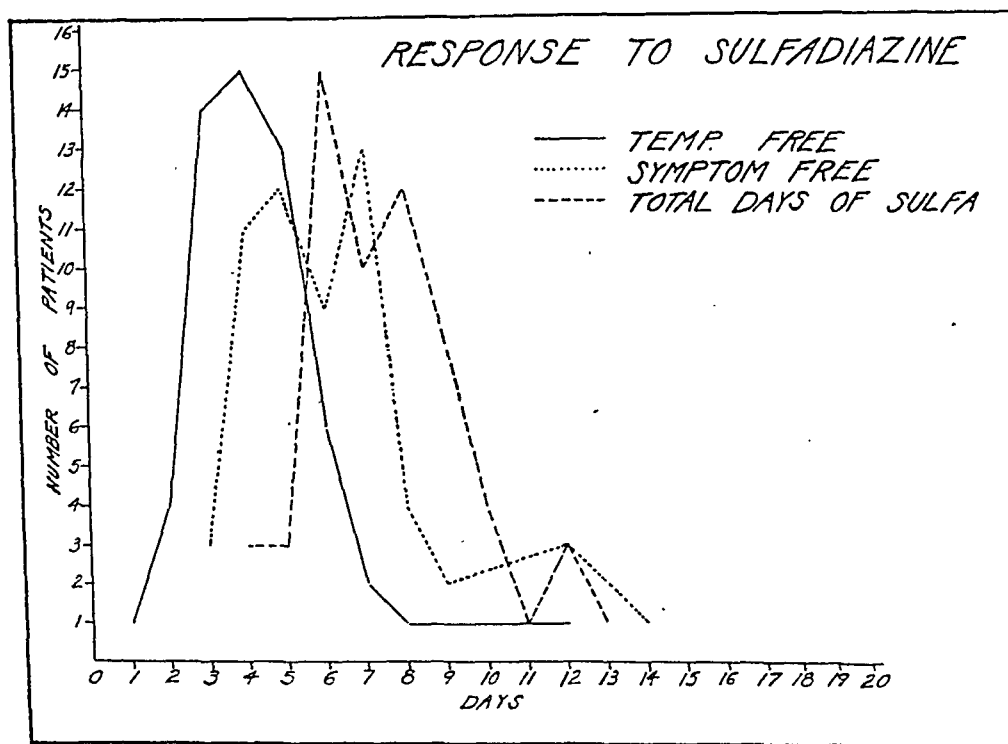


FIG. 3. Response to sulfadiazine in meningococcal infections: comparative duration of fever, symptoms and sulfadiazine therapy.

level was higher than 15 mg. per cent in some, whereas in others the sulfa level was lower than 5 mg. per cent. The therapeutic effect in those patients having a high level and in those having a low level was apparently the same, nor was there any time difference in the freedom from fever and symptoms in the high and low sulfa level groups.<sup>16</sup> It was noted, however, that patients receiving larger quantities of fluid frequently had lower sulfadiazine levels.<sup>17</sup>

Sulfadiazine blood levels were taken on each patient every second day during the first six days after treatment was begun. The average level attained was 8.7 mg. per cent, the lowest being 1.1 mg. per cent, and the highest 19.0 mg. per cent.

## CONVALESCENCE AND REHABILITATION

Despite the acute course of most meningococcal infections, the average patient becoming symptom-free in 6.2 days, it has been our practice to continue hospitalization for a much longer period. This insures the patient adequate convalescence and affords the opportunity of observing him for the possible development of late complications. At periodic intervals during his convalescence and immediately prior to discharge from the hospital he is given careful neurological, orthopedic and ophthalmologic examinations.

The average total hospital days per patient were 44.1. The longest period of hospitalization was 69 days, whereas the shortest was 15 days.

Following the acute phase of the illness each patient was started upon a program of mental and physical rehabilitation including arts and crafts, graduated physical exercises and light duties. At the time of discharge most patients had been completely rehabilitated and were ready for full military duty. Although the average number of hospital days in our group is similar to that of other Army installations, it is slightly higher than is reported by most civilian hospitals. However, the figures of the two groups are not comparable as most of our patients are completely rehabilitated during convalescence in the hospital and upon discharge are capable of performing full military duty, whereas patients discharged from civilian institutions more commonly are required to complete the terminal phase of their convalescence at home. The importance of such rehabilitation has been adequately demonstrated by the splendid results obtained in the reconditioning program of the Medical Department of the United States Army.<sup>18, 19</sup>

## COMPLICATIONS

Table 1 tabulates the early and late complications encountered in our patients. The findings, in most instances, were mild and transitory in character. Neurological complications included: persistent headache, 3 cases; ptosis of the eyelids, 2 cases; low back pains, 2 cases; anesthetics and paresthesias, 1 case; diplopia and strabismus, 3 cases. Other complications encountered were: toxic myocarditis, 1 case; sinus bradycardia, 1 case; synovitis, 1 case; arthritis, 1 case; myositis, 1 case; and herpes simplex, 16 cases. It may be noted that herpes simplex was present in 25.4 per cent of all patients. However, it is apparent that it was of no diagnostic aid in early diagnosis as in 13 of the 16 cases the condition appeared from two to six days following admission to the hospital when the patients were already recovering. In only three instances was it present upon admission.

Toxic manifestations following the use of sulfadiazine included: sulfacrystalluria, 22 cases; microscopic hematuria, 5 cases; casts, 3 cases; kidney colic, 1 case; oliguria, 1 case; anemia, 1 case; rash, 2 cases; and cyanosis, 1 case. Urinary symptoms were troublesome in character in only two cases; namely, in one case each of oliguria and kidney colic, both of which responded readily to treatment. A moderate number of patients showed

TABLE I  
Complications and Sequelae of Meningococcal Infections

*Transitory Complications  
Due to Disease*

Headache—3  
Ptosis of eyelids—2  
Strabismus—2  
Low back pain—2  
Diplopia—1  
Sinus bradycardia—1  
Myocardial damage—1  
Synovitis—1  
Anesthesia and paresthesia—1  
Transitory myositis trapezius muscle—1  
Arthritis right hand—1  
Herpes simplex—16

*Sequelae*

Residual sciatica, left, mild—1  
Sacro-lumbar pains—1  
Headache—1  
Post-meningitic syndrome, manifested by slow speech,  
moroseness and unfriendliness—1  
Pain and anesthesia of right arm and right leg—1

*Due to Drug*

Sulfa crystalluria—22  
Microscopic hematuria—5  
Hyaline casts—3  
Rash—2  
Kidney colic—1  
Oliguria—1  
Anemia—1  
Cyanosis—1

crystalluria. In most of these, however, only a few crystals were present in the urine. This applies equally to the group with microscopic hematuria. Gross hematuria was not encountered. All of the above mentioned findings occurred during the acute state of the illness or in early convalescence. At the time of discharge from the hospital they had completely disappeared.

A small group of cases, five in number, had minimal residual findings at the termination of hospitalization. One patient had a mild post-meningitic syndrome manifested by slow speech, moroseness and unfriendliness. The other patients in this group had one of the following conditions: mild left sciatica, occasional lumbo-sacral pain, persistent dull headache and recurrent aches and anesthetics of the right arm and leg. All of the above five patients represent a group which delayed entering the hospital for from three to six days following the acute onset of signs and symptoms. It is our belief that these complications might have been prevented if sulfonamide therapy had been started early in the course of illness. This belief is substantiated by the fact that in 26 severe or fulminating cases and in 32 average or mild cases in which treatment was started promptly there were no sequelae.

## DISCUSSION

Detection of the disease in its initial phases was of great concern to us because of our responsibility in certifying to the health of troops immediately prior to overseas movement. As many organizations were under our jurisdiction for only a few days before embarkation, any delay on our part in establishing a diagnosis might have resulted in the inclusion of contacts and carriers in the shipment. Crowding of men on transports being unavoidable, the presence of such foci would have been potentially dangerous. Ac-



cordingly, we attempted to differentiate between early and late signs in the hope that we would be able to find certain criteria which would assist in establishing a diagnosis before the disease had fully developed. It was found that the earliest signs and symptoms included nasopharyngitis, fever, headache; malaise, vomiting, myalgia and arthralgia. In themselves these findings were not significant but when they did occur a diagnosis of meningococcal infection was considered. Although many of the findings commonly associated with meningitis were present very early in the disease they were of much less frequent occurrence than those mentioned above.

Nuchal tenderness, splinting or rigidity and petechiae were the first definite leads to specific diagnosis. The other so-called classical signs in most cases became evident from one-half day to several days later.

Although over 50 per cent of our patients were admitted for other conditions with findings too meager to establish a correct diagnosis, the progress of the disease in others was so rapid as to present no great diagnostic problem. Not infrequently patients were admitted with a history of having been ill for less than 24 hours and upon examination presented a multiplicity of signs including coma, nuchal rigidity, petechiae, Kernig's and Brudzinski's signs, nystagmus, ankle clonus, diaphoresis and herpes.

Bacteriologic diagnosis was established by the isolation of the meningococcus either from the blood stream or from the spinal fluid. All cases suspected of having a meningococcal infection, including those in which meningococcemia alone was suspected, were subjected to a diagnostic spinal puncture. It has been observed by others<sup>17</sup> as well as ourselves that the organism may invade the meninges early and examination reveal a clear spinal fluid and minimal neurological signs. A stained spinal fluid smear in such cases not infrequently is found to be positive, thus establishing a diagnosis far in advance of confirmation by a positive blood culture with the resultant earlier institution of treatment.

Immediately following diagnosis sulfadiazine and its sodium salt were given in sufficiently large doses to secure a high concentration of the drug in the blood stream in the shortest possible period of time. It is our belief that the first 24 hours are the most important in the treatment of meningococcal infections and consequently more intensive therapy is required during that period for the following reasons:

1. The growth and proliferation of the organism is inhibited.
2. The tissue damage associated with the disease is checked, thus minimizing complications.
3. The necessity of giving large doses of sulfonamides on succeeding days is avoided.
4. The number of days of therapy is reduced.
5. Sulfa-fastness is prevented by giving adequate dosage in the initial phase of treatment.

Many papers have appeared in the medical literature with regard to optimum sulfonamide dosage in meningococcal infections. Harries<sup>8</sup> in 1942 reported 500 cases which were treated with sulfapyridine and sulfathiazole. His original total dosage was 28 gm.; however, after 250 cases had been treated the dosage was increased to approximately 38 gm. to diminish recurrences and septicemic complications. A small percentage of sequelae and a negligible percentage of toxic reactions from sulfa therapy were reported by this author. It is interesting to note that, although the total mortality was 8.6 per cent, in the age group of 15 to 25 years the mortality was less than 1 per cent. In its upper level this approximates the average age (26.6 years) of our own series as well as that of others<sup>20</sup> who report this as the most favorable age group from the standpoint of prognosis. In contrast to the low dosage mentioned above, Marangoni and D'Agati,<sup>21</sup> working with soldiers in favorable age groups, gave massive doses of sulfadiazine in amounts as high as 245 gm. and averaging 68 gm. Their mortality, exclusive of three patients who died within 12 hours following admission, was 3.1 per cent. Toxic reactions due to sulfonamides occurred in 28 per cent of their cases and included gross hematuria, kidney colic, anuria, oliguria and hemolytic anemia. Daniels, Solomon and Jaquette,<sup>2</sup> in a series of 112 cases with only one death, divided their patients into two therapeutic groups, one of which received an average total dosage of 87 gm. of sulfadiazine and the other 54 gm. They found no better therapeutic response from the use of the larger than from the smaller dose, and also found that the larger dose was more prone to cause kidney and other toxic sulfonamide manifestations not found in the group in which the smaller dose had been used. In our own series the average amount of drug employed (54.7 gm.) and the favorable results obtained closely resemble those of the small dose group of the investigators mentioned above<sup>2</sup> and is evidenced by the absence of mortality, the short febrile period, the short duration of clinical manifestations, the short period required for drug administration, the small number of toxic drug reactions and the small number of residual complications.

We feel that, in view of the above considerations, the optimum total dose of sulfadiazine in most cases of meningococcal infection lies between 50 and 60 gm.

#### SUMMARY AND CONCLUSIONS

1. Sixty-three consecutive cases of meningococcal infections were treated at an Army port of embarkation hospital during the period from July 4, 1942 to July 4, 1945. This group represents the total incidence in slightly over one million processed seasoned troops.
2. The disease was sporadic in occurrence. Diagnosis is frequently difficult and delayed in inter-epidemic periods. The value of early signs and symptoms in establishing a diagnosis is emphasized.

3. Therapy is most effective during the first 24 hours. All patients, regardless of their clinical appearance, must be considered seriously ill and treated accordingly. Intravenous therapy is the most rapid and satisfactory means of securing a therapeutic sulfonamide effect. Sodium sulfadiazine is recommended as the drug of choice for initial medication in all cases of meningococcal infection regardless of severity. Sulfadiazine and its sodium salt were the only chemotherapeutic drugs used. The average total dose per patient was 54.7 gm. No correlation was found between blood sulfadiazine concentrations and the clinical response obtained.

4. Complications due to the disease and toxic reactions following the use of sulfadiazine were negligible. All patients were returned to duty.

5. No fatalities occurred among the 63 cases reported.

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# MENINGOCOCCEMIA: A DESCRIPTION OF THE CLINICAL PICTURE AND A COMPARISON OF THE EFFICACY OF SULFADIAZINE AND PENICILLIN IN THE TREATMENT OF THIRTY CASES\*

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MENINGOCOCCIC infections are notoriously more prevalent in time of war, and during the past four years a relatively high incidence has been noted in army camps. This has afforded an unusual opportunity to study some of the less frequent forms of these infections. When the meningococcus localizes in the meninges there develops a clinical picture which presents no difficulty in diagnosis. If, however, the organism does not localize but remains active only in the circulating blood, the diagnosis is frequently overlooked. Although meningococcemia has been recognized with increasing frequency during the past few years, yet by 1943 there had been only 88 instances reported in the American and British literature.<sup>1</sup> Of these, the great majority were of the chronic variety in which the symptoms had persisted for a comparatively long period of time before the cause was recognized. Since that time cases of acute meningococcemia have been reported with increasing frequency, indicating that the diagnosis is being made much earlier in the disease. This form of the infection has been particularly common in army camps, and at this Post, in a period of 31 months out of the past three years, 33 proved cases were observed, and at least 29 cases were seen in which the diagnosis was not confirmed bacteriologically but in which the clinical picture was so characteristic that they can be considered as instances of meningococcemia. During the same period 111 patients with meningococcic meningitis were seen. Thus, at this Post, for every two cases of meningitis, there was approximately one case of meningococcemia without meningitis. This emphasizes the point that this form of infection is one of the most common types of disease produced by the meningococcus.

As a result of the profession's increasing awareness of this form of the disease, and because of the impetus given to its study by its comparatively high incidence in army camps, the clinical pattern of meningococcemia is emerging more distinct. It is now possible to make the diagnosis clinically without bacteriologic proof, with reasonable certainty, the most essential prerequisite being to think of its possibility.

This paper describes the clinical features of meningococcemia as seen in a group of cases in which the diagnosis was proved bacteriologically, and

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compares this group with another group in which it was not confirmed; in both groups every patient was under the care and treatment of the same medical officer.

The therapeutic efficacy of sulfadiazine in meningococemia is well established.<sup>2, 3, 4, 5, 6</sup> However, no reports of its treatment with penicillin have been seen. The present report compares the relative virtues of sulfadiazine and penicillin as therapeutic agents.

### CLINICAL MATERIAL

Between February 1944 and June 1945, there were admitted to this hospital 61 patients with meningococcal infection, of whom 31 had meningitis, 15 had proved meningococemia, and 15 had unconfirmed meningococemia. The latter group of 30 cases of meningococemia, confirmed and unconfirmed, constitutes the basis for this report. The age range was from 18 to 38 years, the average \* being 24. One patient was a negro, the others white. The average duration of military service was three months. Nine of these cases occurred in January, four in February, three in March, three in April, two in May, four in June, three in July, one in September and one in October.

### PROVED MENINGOCOCCEMIA

*Clinical Picture:* There were prodromal symptoms in every instance (table 1): 11 patients had acute upper respiratory infections averaging one day in duration, and every patient had some fever, averaging one day in duration. In nearly every case, the acute illness was ushered in by chills, increase in fever, and headache. A rash developed in every patient but one. Two-thirds of the patients had nausea and vomiting, and three-quarters of them had joint pains. The admission temperature ranged from 99° to 104° and the highest temperature from 102° to 105°. The headache was conspicuously different from the generalized "splitting" or "bursting" type so characteristic of meningitis: it was throbbing in nature and usually frontal in distribution.

Although the characteristic eruption in meningococcal infections has generally been considered to be one of a hemorrhagic nature, yet in the cases of meningococemia here reported, the typical lesion was a maculopapular one. Many of the macules took the form of pink plaques similar to the "rose spots" of typhoid fever. These varied in size from 2 or 3 millimeters in diameter to areas of 10 to 12 square centimeters. In approximately half of the patients, hemorrhagic lesions were also present in the form of petechiae or purpuric spots; frequently these petechiae appeared in the center of the macules. Several patients exhibited all varieties of the rash concomitantly. Many of the lesions were tender to pressure, especially the hemorrhagic forms. In some cases only a few indistinct and isolated spots were present,

\* Throughout this paper wherever the word "average" is used, it is actually the median, which gives a more accurate picture of the actual situation than would the true average.

TABLE I

Pertinent clinical and laboratory data in 15 patients with acute meningococemia, proved bacteriologically. The cases are divided into sulfadiazine-treated and penicillin-treated groups. Medians are used instead of means to express the "average"

Case No.	Age	Length of Service		Prodromata		Symptoms and Signs							Laboratory		Duration (After treatment was begun)	
		Mos.	URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity	Blood Cult.	Leuko-cyte Count	Fever	Rash
			days	days								1	2		hours	days
Sulfadiazine Treated																
1	20	4	0	.5	0	x	x	x	x	x	x	x	1	19,000	12	2
2	21	15	12	10	0	x	x	x	x	x	x	x	1	14,000	12	4
3	19	0	14	1	x	x	x	x	0	0	x	x	1	13,000	12	3
4	24	3	1	.3	x	x	x	x	0	0	x	x	1	16,000	24	1
5	31	36	5	3	x	x	x	x	x	x	x	x	1	12,000	48	2
6	19	3	1	.5	x	x	x	x	0	x	x	x	1	13,000	24	2
Median or %	21	3.5	3	1	67%	100%	100%	83%	67%	100%	33%	67%		13,500	18	2
Penicillin Treated																
7	20	14	12	11	x	x	x	x	x	x	x	x	1	19,000	12	4
8	18	4	0	21	0	x	x	0	0	0	0	x	1	17,000	4	0
9	24	3	38	4	x	x	x	0	x	x	x	x	1	16,000	12	4
10	34	5	0	2	0	x	x	x	x	x	x	x	1	20,000	0	4
11	18	1	1	1	x	x	x	0	x	x	x	x	1	10,000	12	1
12	26	1	14	6	x	x	x	x	x	0	x	x	1	11,000	12	1
13	25	1	14	1	x	x	x	x	x	0	x	x	2A	13,000	9	2
14	24	2	0	1	x	x	x	x	0	x	x	x	1	25,000	10	1
15	22	3	1	.5	x	x	x	x	x	x	x	x	1	11,000	9	3
Median or %	24	3	1	1.5	78%	89%	100%	89%	66%	78%	89%	44%	56%	16,000	10	2
Entire Group																
	22	3	1	1	73%	93%	100%	93%	67%	73%	93%	40%	60%	14,000	12	2

whereas in others the rash was widespread and coalescent. The most common locations were the shoulders, axillae, arms, chest, legs, abdomen and back, in the order named; the face was not involved in any of the patients. Buccal mucous membrane and conjunctival petechiae were seen in several instances.

*Laboratory Findings:* The leukocyte count varied from 10,000 to 25,000, averaging 14,000, and the percentage of neutrophils from 80 per cent to 96 per cent.

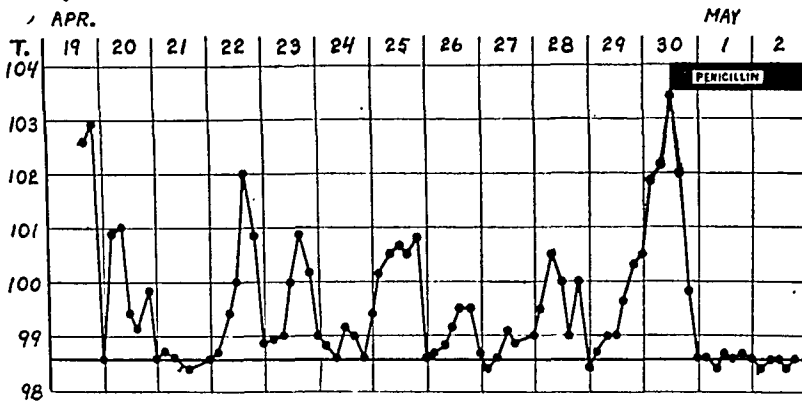


FIG. 1.

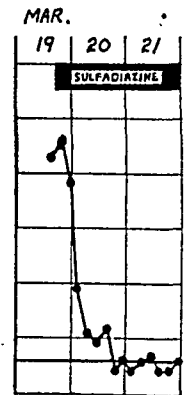


FIG. 2.

FIG. 1. The temperature chart of a patient with acute meningococemia, treated with penicillin. This also illustrates one type of temperature curve seen in this disease. The diagnosis was not made until a rash appeared, on April 30. Blood cultures were later reported positive for the meningococcus.

FIG. 2. The temperature chart of a patient with acute meningococemia, treated with sulfadiazine. The diagnosis was made clinically, shortly after admission, and it was later confirmed by a positive blood culture.

The meningococcus which was recovered from the blood was of Group 1 in 14 cases and of Group 2A in one.

The spinal fluid was examined in 10 patients, on six of whom three punctures were done for the purpose of assaying the fluid for penicillin.\* In every instance the cell count, smear and culture were normal or negative.

### UNCONFIRMED MENINGOCOCCEMIA

The clinical picture in the 15 cases of meningococemia which were unconfirmed bacteriologically, was indistinguishable from that of the proved cases. The length of service, the duration of fever prior to the onset of the acute symptoms, the incidence of upper respiratory infections, chills, headache and nausea, and the leukocyte counts were all essentially the same (table 2). So too was the response to treatment as evidenced by the rapidity of disappearance of the fever and of the rash. The character and distribution of the rash were exactly the same as in the proved cases. The only differences between the two groups were the duration of the respiratory

\* The results of these assays are being reported in a separate paper.



TABLE II  
As for table 1 except that the diagnosis was not confirmed bacteriologically in any of the 15 patients.

Case No.	Age	Length of Service		Prodromata		Symptoms and Signs								Laboratory		Duration (After treatment was begun)	
		URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity	Blood Cult.	Leuko- cyte Count			Fever	Rash
		days	days								1 2	Type				hours	days
Sulfadiazine Treated																	
1	24	8	0	0	x	x	x	x	x	x	x	0	21,000			12	1
2	38	4	9	0	x	x	x	x	0	x	x	0	9,000			20	2
3	25	8	0	0	0	x	x	0	0	x	x	0	15,000			28	1.5
4	20	3	1	14	x	x	x	0	0	x	x	0	10,000		x	24	2
5	19	3	2	.5	0	x	x	0	0	x	x	0	18,000		x	24	3
6	22	2	0	.5	x	x	x	0	0	x	x	0	17,000		x	96	2
Median or %	23	3.5	0.5	1.5	67%	100%	100%	33%	17%	100%	83%		16,000			24	2
Penicillin Treated																	
7	18	2	0	2	0	x	x	x	0	x	x	0	18,000			12	4
8	26	28	7	1	x	x	x	0	x	x	x	0	13,000			8	5
9	24	7	14	2	x	x	x	x	0	x	x	0	13,000			24	2
10	18	1	7	1	x	x	x	0	0	x	x	0	19,000			12	1
11	25	0	4	4	x	x	x	x	x	x	x	0	8,000			72	1
12	18	1	4	4	x	x	x	x	0	x	x	0	18,000			0	1
13	18	3	14	1	x	x	x	x	0	x	x	0	12,000			8	2
14	38	10	21	1	x	x	x	x	0	x	x	0	12,000			6	1
15	33	1	0	1	x	x	x	x	x	x	x	0	12,000			12	3
Median or %	24	2	7	1	89%	100%	100%	78%	44%	100%	56%		13,000			12	2
Entire Group																	
	24	3	4	1	80%	100%	100%	60%	33%	100%	67%		13,000			12	2

infection and the incidence of joint pains. The former can scarcely be considered a significant discrepancy, and evidence will be presented later in this paper to indicate that the lower incidence of joint pains in the unconfirmed cases should not introduce any element of doubt as to the correctness of the diagnosis. It is believed, therefore, that these 15 cases are truly instances of meningococemia.

The spinal fluid was examined in nine of these patients and the cell count, smear and culture were normal or negative in every instance.

### TREATMENT

For therapeutic purposes the 30 patients were divided into two groups without regard to the presence or absence of a positive blood culture. In nearly every case the diagnosis was made clinically and treatment was begun before the result of the blood culture was known. The 12 patients in Group 1 were treated with sulfadiazine and the 18 patients in Group 2 with penicillin. In the first 24 cases treatment was alternated between the two drugs, but the last six were treated with penicillin.

*Dosage:* (1) The initial dose of sulfadiazine was 4 grams, and was followed by 1 gram every four hours. This was continued until a normal temperature had been maintained for 48 hours, the average duration of therapy being four days, with a total dose of 27 grams. The concentration of the drug in the blood varied between 4 and 12 mg. per cent.

(2) In the first four patients, penicillin therapy was started with an intravenous dose of 40,000 units, followed in one hour by 40,000 units intramuscularly. The latter was repeated every three hours for 24 hours, after which 25,000 units were given intramuscularly every three hours for a total treatment period of five days. Since it became evident that that dosage was unnecessarily excessive, the next 13 patients received an initial dose of 25,000 units intravenously, followed by 25,000 units intramuscularly in one hour and thereafter every three hours. The total treatment period was five days except in one patient, in whom it was four days. One patient was treated with a sodium penicillin-beeswax-peanut oil mixture, containing 100,000 units per c.c., 1 c.c. being given intramuscularly, repeated 12 hours later, and then at 24 hour intervals for a total of six doses or 600,000 units.

*Results:* Every patient recovered. Since the mortality rate cannot, therefore, be used as a criterion of the comparative therapeutic efficacy of sulfadiazine and penicillin, other factors must be taken into consideration. Of these, the rapidity of disappearance of fever, of the symptoms and of the rash are of the most value in measuring therapeutic effect. In all of the 30 cases the symptoms usually disappeared within 24 hours after therapy was begun. The objective signs—the rate of disappearance of the fever and of the rash—are a more reliable index (tables 1 and 2). In the six proved cases treated with sulfadiazine the average time required for the temperature to reach normal was 18 hours whereas in the nine proved cases treated with penicillin it was 10 hours; in the unconfirmed group, the average time in the

six sulfadiazine-treated patients was 24 hours and in the nine penicillin-treated patients it was 12 hours. Grouping all the sulfadiazine-treated cases together, the average time was 24 hours, whereas for all the penicillin-treated cases it was 12 hours. Thus the duration of fever following penicillin therapy was 12 hours less than that following sulfadiazine therapy. In both groups the rash disappeared in two days on the average; occasionally the macular plaques would disappear within a matter of hours, though the petechial and purpuric lesions persisted longer. No complications followed either drug.

Two illustrative case reports follow, a representative one from each group:

#### CASE REPORTS

*Case 1.* A 20 year old soldier was admitted to the hospital on April 19, 1944, with a history of a common cold beginning one day previously. On admission his chief complaints were headache, vomiting, and fever, and the temperature was 102.6° F., pulse 114, and respirations 24. Physical examination revealed nothing abnormal except a slight degree of pharyngeal injection. A leukocyte count was 10,500 with 80 per cent neutrophils. The temperature receded to normal on April 21 (figure 1). However, the throbbing headache persisted, and on April 22 he again began to have a moderate fever, the temperature ranging from 98.6° to 102° F., continuing until April 29 when a few pink rose-colored spots appeared on his legs. During the morning of April 30 there was an increase in the headache. The temperature climbed to 103.4° F. On this day also, tender erythematous macules and plaques appeared in crops, still over the legs only. The leukocyte count had risen to 19,000 with 90 per cent neutrophils. Later it was learned that blood cultures done on April 26, 27, 28, 29 and 30 all yielded the meningococcus Group 1. Neurological examination revealed normal findings. At no time had stiffness of the neck or Kernig's sign been present, but a spinal puncture was performed, the fluid being clear and colorless with normal dynamics; it contained no cells and the sugar content was 76 mg. per cent.

Penicillin was administered at 12 noon on this same day (April 30) using the smaller dosage schedule as outlined above. Spinal fluid was obtained eight and 24 hours later, the routine studies being normal and the penicillin assays negative. By 8 p.m. the temperature had dropped to 99.8° and to normal by midnight, remaining so for the duration of hospitalization. The rash disappeared four days after therapy was started. Penicillin had been administered over a five day period with a total dose of 1,025,000 units. Convalescence was rapid and recovery was complete. The patient was discharged from the hospital on May 13, 1944. (Note: This example is typical of the clinical picture of acute meningococemia except for the unusual distribution of the rash.)

*Case 2.* A 24 year old white soldier was admitted to the hospital on March 18, 1944 at 3 p.m. Approximately one day before admission the patient developed an acute upper respiratory infection characterized mainly by soreness of the throat. About 10:45 a.m. on the day of admission he began to feel feverish, and this was followed by generalized muscle aching, shaking chills, dull, throbbing frontal headache and nausea.

On physical examination immediately prior to therapy the temperature was 102.3° F. and the pulse 96. The pharynx was slightly injected and a maculo-papular eruption was noted over the chest and forearms. Several of the lesions had very small petechial centers and these were tender to pressure. A leukocyte count was

16,000 with 86 per cent neutrophiles, and a blood culture later grew the meningococcus, Group 1.

At 6 p.m. on the day of admission therapy was started, consisting of 4 gm. of sulfadiazine by mouth. This was followed by 1 gm. every four hours. The temperature began dropping, and by 6 p.m. of the following day (March 19) it was normal and remained so for the duration of hospitalization (figure 2). By the time the temperature had reached normal the rash had disappeared. Convalescence followed and there were no sequelae. A total of 27 grams of sulfadiazine was administered over a four day period. The patient was discharged on April 1, 1944.

### DISCUSSION

When cases of meningococemia are being seen only rarely there might be an understandable hesitation in making the diagnosis without bacteriological proof. However, when patients in whom the diagnosis has been proved are being seen rather frequently, as is the case in many army hospitals, one develops a high degree of alertness for the disease—a most important essential for its recognition. If one examines the two groups of cases herein reported—confirmed and unconfirmed—it is evident that there are no significant differences in the symptomatology, the physical findings, the clinical course or the response to treatment, between those patients with a positive blood culture and those with a negative one. Moreover, the clinical picture is so characteristic that when a patient is seen who presents all the typical features of the proved cases save only a positive blood culture, there can be little reasonable doubt as to the diagnosis. It should be emphasized that the characteristic rash is a *sine qua non* for making the diagnosis clinically.

It was not so many years ago that meningococemia was considered a rarity. However, it has been reported much more frequently in recent years. The war has given an impetus to its study in that the incidence of meningococcic infections has shown a very great increase, and most of the larger series of cases reported since 1941 have been from army camps. One of the largest groups (32 cases) was reported by Daniels et al.<sup>2</sup> in 1943. Since their patients were seen at the same army hospital as those of the present report, it is of considerable interest to compare certain features of the disease in the two groups; the interest in the comparison is heightened by the fact that their patients were observed during the first four months of 1943, a period when the incidence was somewhat higher than normal, whereas the present authors' cases were seen over a 16 month period in 1944 and 1945 when the incidence was normal for the Post. Certain salient points for comparison between the two groups are set forth in table 3.

The similarity in general of the length of military service, the duration of the prodromal symptoms, the incidence of the different signs and symptoms, and the laboratory findings in the two groups is quite striking. In Daniels' patients, chills, headache and joint pains were not quite so common as in the authors', and more of the former were classified as mild in severity, but the differences are probably not of any great significance. Whereas in the

TABLE III  
A comparison between the authors' 30 cases and 32 cases reported by Daniels, et al.<sup>2</sup> All figures are either medians or percentages.

No. of Cases	Age	Length of Service	Prodromata		Symptoms and Signs								Laboratory		Duration (After treatment was begun)	
			URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity	Positive Blood Culture	Leuko-cyte Count	Fever	Rash
			days	days	days	%	%	%	%	%	%	1 2 3	%		hours	days
<i>Daniels et al.</i> Confirmed 18 Unconfirmed 14 Entire Group 32	22	2	1.5	1	78	61	100	78	72	28	100	61	100	18,250	24	4
	21	1.5	6.5	1	78	29	100	78	43	50	100	93	0	16,400	24	3.5
	22	2	3.5	1	78	47	100	78	59	38	100	75	56	17,600	24	4
<i>Authors'</i> Confirmed 15 Unconfirmed 15 Entire Group 30	22	3	1	1	73	93	100	93	67	73	93	40	100	14,000	12	2
	24	3	4	1	80	80	100	100	60	33	100	67	0	13,000	12	2
	23	3	3	1	77	87	100	97	63	53	97	53	50	13,500	12	2

authors' cases joint pains were much more common in the proved cases than in the unconfirmed ones, in Daniels' cases the reverse was true, indicating that the absence of arthralgia cannot be regarded per se as a valid argument against the diagnosis of meningococemia. It is significant, however, that the illness, as seen during a period when the incidence of the disease was greater than normal, did not appear to be of any greater severity than that during non-epidemic periods—and in fact appeared even milder.

Prior to the present war most of the cases of meningococemia were of the chronic type, which lasted for weeks or months, and the diagnosis was frequently made only when meningitis developed. Since the war presented an opportunity to study comparatively large numbers of cases, the diagnosis has been made much earlier, and recent reports have dealt with the acute rather than the chronic variety of the infection. In one group of cases<sup>7</sup> reported in 1944, symptoms were present not longer than two weeks before the diagnosis was made. In the cases here reported the diagnosis was made within four days of onset, on the average, although in individual instances it required two to three weeks, and in one single case, 38 days to establish it. This point is worth calling attention to, to emphasize the fact that the diagnosis can and should be made very early in the great majority of cases.

There has been some objection on the part of some physicians to performing spinal punctures in cases of meningococemia without meningitis, on the theory that the needle might introduce organisms into the otherwise sterile spinal canal. In the cases reported here no instance was encountered in which meningitis developed following spinal puncture. Of course treatment was begun immediately afterward or had been previously started. Although sulfadiazine could have aborted meningitis, yet experience at this hospital indicates that penicillin parenterally does not always sterilize the meninges. Hence it is concluded that the failure of meningitis to develop indicates that it is probable that spinal puncture is a safe procedure in cases of meningococemia.

As judged by the symptoms, laboratory findings and clinical impression, there was no significant difference in severity between the sulfadiazine and the penicillin treated cases. For the purpose of comparing the effects of therapy the two groups were essentially identical in all respects.

There appears to be little difference between sulfadiazine and penicillin from the standpoint of the rapidity or the degree of response to therapy, although the temperature response to penicillin was somewhat more rapid by approximately a half day. The situation is comparable to that in pneumococcal pneumonia, wherein it has been demonstrated that sulfadiazine and penicillin are of almost exactly equal therapeutic value.<sup>8</sup> The decision as to which drug to employ depends, therefore, on other factors than the therapeutic effect: on the question as to whether the fear of possible toxic effects from sulfadiazine outweighs the nuisance of frequent and painful injections, at present necessary with penicillin; on the patient's ability to swallow and retain the sulfonamide; and on other factors such as sensitivity

of the individual to the sulfonamides, resistance of the meningococcus to the sulfonamides, etc. Should penicillin become available for general use in the form of a beeswax-peanut oil or other mixture wherein only one, or at the most, two injections a day are necessary, or should satisfactory preparations for oral use be developed, it is probable that its factor of safety over the sulfonamides will make it the drug of choice.

### SUMMARY AND CONCLUSIONS

1. Within a 16 month period in 1944 and 1945, there were seen 31 soldiers with meningococcic meningitis; during the same period there were 30 patients in whom the diagnosis of meningococcemia without meningitis was made. Of these 30, the diagnosis was confirmed bacteriologically in 15 and was unconfirmed in 15. The average age was 23 and the average length of service was three months. Most of the cases occurred in the first six months of the calendar year.

2. A comparison is made between the 15 proved cases and the 15 unconfirmed ones. It is shown that except for the blood culture, the clinical picture in the two groups was essentially identical. The average duration of symptoms prior to diagnosis was less than four days; every patient had fever and a rash (one exception); most of them had an upper respiratory infection, chills, headache, and nausea; half of them had joint pains. The typical rash was maculo-papular rather than hemorrhagic, as is generally described.

3. A comparison is made between this series of 15 proved and 15 unconfirmed cases and a series of 18 proved and 14 unconfirmed cases seen at the same hospital in a four month period in 1943 and reported by other authors. There were no essential differences between the proved cases in each series nor between the unconfirmed cases. Moreover, in both series, no appreciable differences could be discovered between the proved and the unconfirmed cases. This lends further support to the conclusion that meningococcemia can and should be diagnosed clinically.

4. Spinal punctures were performed on 19 patients, and three times on six of them. In no instance did meningitis develop. Although the fact that treatment was already under way or was instituted shortly after could have prevented infection of the meninges, yet, since penicillin given parenterally does not always sterilize the meninges, it is concluded that spinal puncture in meningococcemia is a safe procedure.

5. Twelve of the patients were treated with sulfadiazine and 18 with penicillin. Therapeutic results were identical except that the temperature reached normal 12 hours earlier in the penicillin-treated group than in the sulfadiazine-treated group.

*Addendum:* Since the above paper was submitted, a patient has been seen who developed meningitis while she was under penicillin therapy for meningococcemia without meningitis. She recovered promptly when sulfadiazine was administered. This is the only instance of this occurrence to come to the attention of the authors, either from personal observation or from hearsay.

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# POST-DIPHTHERITIC POLYNEURITIS: A REPORT OF FIVE CASES WITH ALBUMINOCYTOLOGIC DISSOCIATION SIMULATING GUILLAIN-BARRÉ'S SYNDROME\*

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It seems highly probable that many cases of diphtheritic polyneuritis are being improperly designated as a primary neurological disease, and being erroneously catalogued variously as: infectious polyneuritis, radiculoneuritis, or Guillain-Barré's syndrome. Review of the present literature and personal observation in retrospect adds confirmation to this belief. We are here reporting five cases manifesting several interesting features with one common finding—albumino-cytologic dissociation—in order to emphasize the ease with which they could have been dismissed in a like manner. In all respects these cases satisfy the original criteria set up by Guillain, Barré and Strohle<sup>1</sup> of polyneuritis, normal spinal fluid cell counts and increased cerebrospinal fluid protein, existing in patients with an ultimately favorable prognosis. In spite of the fact that these cases fall so clearly within this group, the diagnosis of preëxisting diphtheria can not be reasonably doubted.

Diphtheria rarely reaches epidemic proportion at the present time and the failure to recognize it is all the more likely since one is dealing with sporadic cases. Moreover, the neuritic symptoms frequently appear as a late complication after the initial infection has subsided undiagnosed. Signs, symptoms, bacteriology and the treatment for diphtheria have been known for years, but there seems to be a modern tendency to disregard the immediate and remote dangers of this serious disease. A high percentage of our children are well protected against diphtheria by active immunization, but a huge segment of the young adult population has no such defense. As with all communicable diseases, diphtheria has taken on new significance in war time.

The syndrome of polyradiculoneuritis with albumino-cytological dissociation of the spinal fluid was described by Guillain, Barré and Strohle in 1916. Their original report was based on the study of two cases. Since that time numerous reports of similar cases have appeared: for example, by Casamajor,<sup>2</sup> Bradford, Bashford and Wilson,<sup>3</sup> Kennedy,<sup>4</sup> Baker,<sup>5</sup> Jervis and Strassburger,<sup>6</sup> Shaskan,<sup>7</sup> and others. The syndrome has become well recognized and widely accepted. Correctly or incorrectly, it has been referred to as a disease entity probably resulting from infection with a neurotropic virus. The confusion attendant to acceptance of the syndrome as a specific entity

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is clearly shown by all writing upon the subject. Jervis and Strassburger describe a case presenting the characteristics of Guillain-Barré's syndrome yet they felt the pathological anatomy was definitely that of anterior poliomyelitis. De Jong<sup>8</sup> has questioned whether any of these polyneuritic syndromes belong to a single group of disorders or constitute a disease entity. Ederle<sup>9</sup> has raised similar doubts. That the nervous system sequelae of diphtheria be classed within the syndrome of "radiculoneuritis" with acellular hyperalbuminosis of the cerebrospinal fluid is quite acceptable. It is not acceptable that the possible primary etiology, infection with *C. diphtheriae*, go unrecognized. All such cases should be thoroughly investigated before being dismissed as a primary neurological disease. We believe the cause of good medicine is served by such insistence.

#### CASE REPORTS

*Case 1.* This 24 year old white male was seen first on March 8, 1945 at which time he was complaining of weakness, difficulty on swallowing, and dermatitis. In July 1944, while serving in the Southwest Pacific, this patient developed a dermatitis which, although not disabling at the time, finally required hospitalization in November 1944. The dermatitis responded to treatment rather promptly. During this time, the patient had some mild difficulty with his eyes. He apparently was unable to accommodate properly. Approximately one month later a flareup of the original dermatitis, aggravated by secondary infection, required further hospitalization. On this admission the patient was treated with colloid baths and parenteral penicillin. Again the dermatitis responded to treatment and all except a few isolated lesions, including one on the left lower leg and several about the perineum, disappeared. On February 7, 1945 the patient, while still hospitalized, developed a very sore throat with formation of a left peritonsillar abscess. He received sulfonamides, the abscess drained spontaneously, and recovery seemed to be good. On February 18, 1945, 10 days after the onset of his acute tonsillitis, the patient noted difficulty on swallowing with regurgitation of liquid through his nose. Two days later weakness of his legs, mild shortness of breath, and a definite nasal voice developed. These symptoms were soon followed by tingling and numbness about the lips, the hands, the feet, and legs. He rapidly became very weak and barely able to sit up without aid. Such were the complaints at the time the patient was first seen here. In general appearance the patient seemed to be undernourished, very pale, sweating profusely and quite short of breath. On first examination the pulse rate was 120, blood pressure 96 mm. Hg systolic and 76 mm. diastolic, and an easily detectable gallop rhythm was present. In any other than a completely prone position, the patient exhibited profound vascular collapse and his blood pressure could not be determined. The neurological examination at that time revealed a nasal voice, complete paralysis of the right palate, partial paralysis of the left palate, failure of the right eye to converge, subjective difficulty in focusing, bilateral lower facial weakness, intact light touch sensation, pronounced hypalgesia over the face, extremities and trunk except for the ninth to twelfth thoracic dermatomes. There was marked weakness, marked fatigability and diffuse atrophy pronounced in the proximal girdle muscles. Tendon jerks in the upper extremities and ankle jerks were weakly active, knee jerks were absent, corneal and abdominal reflexes were normal as was the plantar reflex. The skin was quite clear except for some residual dark pigmentation. However, there was a healed lesion on the left lower leg resembling a healing ulcer approximately 1 cm. in diameter. Directly over the tip of the coccyx was an ulcer approximately 1 cm. in diameter and 1 cm. in depth. This lesion

was covered with a heavy crust of exudate and yielded cream-colored pus. The walls of the ulcer were covered with a gray tenacious membrane.

Smears and cultures from the throat and from the ulcer described above yielded numerous colonies of *Corynebacterium diphtheriae* of marked virulence for the guinea pig. The electrocardiogram showed a remarkably reduced voltage in all leads with a prolongation of QRS time characteristic of arborization type of intraventricular block. Other routine laboratory examinations, including blood counts, serologic reactions, routine blood chemical tests and urine examination, were normal with the exception of the white blood cell count. The initial white blood cell count was 16,200 with an essentially normal differential count. Examination of the cerebral spinal fluid showed a normal cell count with a spinal fluid protein of 215 mg. per cent.

With the diagnosis of post-diphtheritic paralysis and myocarditis thoroughly established, this patient was treated with 100,000 units of diphtheria antitoxin immediately. In addition to this, he was treated with penicillin in dosages of 10,000 units every two hours. Local applications of penicillin in aqueous solution to the cutaneous lesion were made frequently. Supportive therapy with adrenal cortical extract was also given during the critical state of his illness. Within a period of 10 days the myocardial lesion had largely subsided. The paralysis became more profound and the patient did not reach the peak of his disability until March 30, 1945. It was then noted that the palatal paralysis began slowly to subside. Subsequently a gradual return of the sensory and motor function of the extremities supervened. By July 1, 1945 patient was able to walk unaided. The cutaneous lesion, even with the topical application of penicillin in addition to the parenteral antitoxin, required about three weeks to heal. The lesion became negative for *C. diphtheriae*, however, within a matter of three days.

This case is of interest for several reasons: (1) It seems highly probable that this patient's initial lesion was one of cutaneous diphtheria and that his pharyngeal diphtheria was secondary. (2) The patient developed ocular palsies of transient character during one episode of dermatitis with mild improvement only to succumb to an overwhelming load of toxin from the combined cutaneous and pharyngeal lesions three and one half months later. (3) A severe myocarditis as shown by a gallop rhythm and extensive electrocardiographic disturbance was rendered more disturbing by the marked loss of peripheral vasomotor tone.

*Case 2.* This 19 year old male was first seen April 15, 1945. A casual from convalescent furlough, he presented himself on the third day of his illness complaining of a severe sore throat. Previous attempts to incise a peritonsillar abscess had resulted in no relief. The patient had the usual complaints of malaise, general muscular and body aches and fever. He was obviously acutely ill. His temperature on admission was 103° F., pulse 108, blood pressure 118 mm. Hg systolic and 80 mm. diastolic. He had a bilateral cervical adenopathy and marked swelling of the pharyngeal tissues on the left. There was no evidence of a definite membrane. Throat smears revealed a suspicious organism and when checked *C. diphtheriae* was isolated. This organism proved to have a high degree of virulence for the guinea pig. With identification of the organism on the fourth day of the patient's illness, he was given 60,000 units of diphtheria antitoxin in addition to the parenteral penicillin which he was already receiving. Improvement in the patient's general condition was prompt but on the tenth day of his illness he complained of difficulty on swallowing. He evidenced a nasal twang to his voice and had some failure in visual accommodation. Examination at this time showed obvious palatal paralysis bilaterally and a mild ocular palsy.

These findings remained fairly constant for the following days but by the twenty-eighth day of his illness the patient began to complain of paresthesias of the fingers, hands and arms, as well as of the feet and legs. No motor disability of the extremities developed.

Routine laboratory examination of this patient showed nothing unusual other than a white cell count of 15,200. The isolation of *C. diphtheriae* and proved virulence of this organism were as reported above. A preliminary examination of the spinal fluid showed a cell count of 2 with a spinal fluid protein of 57. The spinal fluid was again examined when the patient first complained of paresthesias in the extremities. Again the cell count was 2, and the spinal fluid protein was 92 mg. per cent.

Five weeks after the onset of paralysis, which had at no time become severe, the patient began to show steady improvement. The palatal paralysis first disappeared and was soon followed by progressive decrease in the paresthesias of the extremities. The only treatment given other than that mentioned above was in the form of a high caloric, high vitamin diet supplemented by the use of vitamin B complex parenterally.

This case represents a mild case of post-diphtheritic polyneuritis developing even though antitoxin was given. It is to be noted, however, that the antitoxin was given on the fourth day following the initial signs of infection. Here the spinal fluid did not show the characteristic albumino-cytologic dissociation when first examined. As the paralysis became more severe, the spinal fluid protein became elevated.

*Case 3.* This 31 year old white male was first seen May 25, 1945. His presenting complaint was one of weakness. A prisoner of war for a period of four months, he had been released on March 29, 1945 with these complaints. At the time the patient was first seen here he was actually slowly recovering. A recapitulation of the history shows that about February 15, while a prisoner, the patient developed a severe sore throat. Associated with the sore throat, the patient had a severe diarrhea. He was aware of the presence of a diphtheria epidemic in the camp in which he was held during the development of his own symptoms. His illness was reported but was not considered severe enough to warrant medication. No smears or cultures were taken. On March 29, 1945, the patient developed a left-sided pleurisy associated with pneumonia. On this occasion he was hospitalized and received treatment with sulfonamides. He promptly improved from his pulmonary complaints. Simultaneously with the onset of his pneumonia he began experiencing difficulty in swallowing, double vision, regurgitation of liquids through his nose, and tingling and numbness of all extremities. The patient had lost 60 pounds during his imprisonment and he considered the new symptoms only a part of his general debility. Upon being seen at this hospital the patient showed evidence of a great weight loss. He spoke with a nasal voice and evidenced marked weakness of the extremities and rather pronounced ataxia. Examination revealed a diminution in position sense, mild ocular palsy, loss of knee and ankle jerks, marked decrease in sensation in the extremities, particularly of the hands and feet. Examination of the cardiovascular system revealed nothing of importance. The blood pressure was 132 mm. Hg systolic and 80 mm. diastolic, pulse 80. The left pleura was considerably thickened and there was a small amount of fluid in the left pleural cavity. A diagnosis of post-diphtheritic paralysis was made on these findings and history. The routine laboratory examination showed nothing remarkable. The roentgenographic examination of the chest showed a moderately dense pleural thickening in the lower chest. No pulmonary disease could be demonstrated. Electrocardiogram was normal. The spinal fluid showed no white blood cells. The spinal fluid protein was 230 mg. The spinal fluid Wassermann reaction was negative.

No specific therapy was given this patient. He was placed on a high caloric, high vitamin diet supplemented with parenteral vitamin B complex. He made a rapid gain in weight and showed progressive diminution in all neurological symptoms and signs.

This patient developed a polyneuritis during a bout of pneumonia complicated by pleural effusion. It is important to note that this paralysis became apparent six weeks after the onset of a sore throat in a prisoner of war camp where diphtheria existed in epidemic form. No specific therapy was given at any stage in the illness.

*Case 4.* This 26 year old white male was first seen at this hospital on May 26, 1945. His presenting complaints were extreme weakness, tingling and numbness of the lips, arms, hands, feet and legs. On April 9, 1945, while this patient was a prisoner of war, he developed a severe sore throat. Two days later when seen by a physician a diagnosis of diphtheria was made. Some form of sulfonamide therapy (probably prontosil) was prescribed. Six days after the onset of the infection he was liberated as a prisoner. He then received 200,000 units of penicillin, sulfadiazine, and 40,000 units of diphtheria antitoxin. Cultures taken from throat smears on this date were positive for *C. diphtheriac*. The therapy was followed by prompt relief of all symptoms associated with his sore throat. Approximately five weeks after the onset of the patient's disease he noted diplopia and difficulty in accommodation. These symptoms were slowly progressive. By May 23, 1945 the patient developed a nasal voice, regurgitation of fluids through the nose and paresthesias of all extremities. These symptoms were becoming steadily more marked when the patient was first seen here. On examination the patient appeared to be in a fair nutritional state. He showed only mild difficulty in visual accommodation but did show rather marked weakness of all extremities. Taste sensation was largely lost. Two point touch discrimination was markedly disturbed. Vibratory and proprioceptive sensation was gone from the waist down. Sphincteric control was only partially adequate. The patient was quite unable to turn himself in bed, feed himself, or sit up. Routine physical findings were essentially normal. The cardiovascular system presented no changes. Blood pressure was 130 mm. Hg systolic and 82 mm. diastolic, pulse 80. The routine laboratory reports showed nothing remarkable. The electrocardiogram was normal. The cerebrospinal fluid showed a cell count of 1, a negative Wassermann reaction, and a protein of 127 mg. per cent. Four weeks later the protein had increased to 154 mg. per cent.

No specific therapy was given to this patient. During the first week of observation the patient continued to grow more completely disabled. He then began slowly to improve. He was given a high caloric, high vitamin diet supplemented with parenteral vitamin B complex. In addition he was given the usual physical therapy.

This case represents one in which the diagnosis of diphtheria was made early in the disease and was later proved by bacteriological studies. Treatment, however, was not made available until the ninth day of his illness. After five weeks of relative freedom from symptoms of any type, the patient began to show mild signs of neurological involvement with rapid progress to a state of complete disability.

*Case 5.* This 32 year old white male was first seen June 25, 1945, at which time he complained of weakness, tingling and numbness of feet, legs and hands. He actually made no mention of complaints except upon questioning, taking them as simply a part of his recent experiences. On December 22, 1944 this patient was taken

prisoner and on March 29, 1945 he was liberated. During this period the patient had an inadequate diet resulting in an estimated loss of 40 pounds. During February 1945 he became infested with lice and developed many indolent pustular skin lesions on the arms and legs. These lesions persisted. When liberated the patient was markedly exhausted, weak and exhibited besides his malnutrition many skin lesions and a low grade fever. He now recalls unusual weakness in the legs and describes paresthesias of the extremities, face and lips. He was placed on a high caloric and vitamin intake, given intravenous glucose and received 340,000 units of penicillin during the first three days of freedom. Sulfadiazine ointment was applied to the skin lesions. In general the patient improved rapidly but remained weak. This he did not consider unusual. He reported no unusual symptoms to his attending physicians. By May 20, 1945 his weakness and paresthesias of the extremities were quite distressing but sensory disturbances about the mouth had gone. The skin lesions were healing although leaving deep, pitted scars surrounded by a broad areola of brownish pigmented skin. On the date first seen here only one ulcer on the antero-lateral surface of the lower left leg remained. Examination of the patient revealed only a fair state of nutrition, with a weight of 135 pounds, whereas normal weight was about 160 pounds. Numerous healed scars of ulcers appeared on lower legs and arms. One ulcer on the left leg remained open. This lesion was shallow and had no membrane or unusual identifying characteristics. Routine physical findings were normal. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The heart and lungs were not unusual. Neurological findings were as follows: Cranial nerves normal, unsteady gait, increased tenderness of muscle masses of arms and legs. Poor coordination of finger to nose and heel to shin test. Triceps reflex very weak; all other tendon reflexes absent; no pathological reflexes. Vibratory sensation markedly diminished at ankles and slightly at wrists. Diminished sensitivity to pin point stimulation over distal portions of arms and legs. Light touch was recognized in all parts of body but was associated with paresthesia over distal parts of extremities. Routine laboratory findings were normal in all respects. Initial spinal fluid examination showed no cells and a protein of 67 mg. per cent. Subsequent examination four weeks later showed 4 cells and protein of 41.9 mg. per cent. Cultures from the open cutaneous lesion showed characteristic *C. diphtheriae*, which proved to be virulent for guinea pig. Progress was slow, but steady improvement continued on a high caloric, high vitamin diet supplemented by parenteral vitamin B complex. Topical penicillin to the ulcer was followed by prompt healing. At no time was the patient's disability great.

This represents a clear cut case of cutaneous diphtheria producing a polyneuritis in which the diagnosis of malnutrition and avitaminosis was not sufficient to account for all the neurological findings. The true nature of this feature was belatedly made only by bacteriological studies. Previously recognized and checked through several hands, these findings of polyneuritis had been repeatedly designated as due to avitaminosis.

In the past history of none of the patients was there evidence of immunity to diphtheria conferred either by the disease or active immunization. The Shick test on each at this late stage was negative. In cases 1, 2 and 4, the Shick test was invalidated by the recent administration of diphtheria antitoxin. Uniform bacteriological studies including stained smears, cultures and guinea pig inoculation for virulence determination, were carried out on cases 1, 2 and 5. The other cases presented no lesions lending themselves to such study.

Case	Spinal Fluid Cell Count	Spinal Fluid Protein
1	0	214
2	2 2	57 92
3	0	230
4	1	127
5	1	67

TABLE SHOWING PROMINENT NEUROLOGICAL FINDINGS

	Case 1	Case 2	Case 3	Case 4	Case 5
Muscle weakness	+	0	+	+	+
Muscle tenderness	+	0	+	+	+
Ataxia	+	0	+	+	+
Loss of deep reflexes	+	+	+	+	+
Loss of superficial reflexes	+	0	+	+	+
Hypesthesia	+	+	+	+	+
Loss of vibration sense	+	+	+	+	+
Loss of light reflex	+	0	+	+	-
Loss of accommodation	+	+	+	+	-
Loss of convergence	+	0	+	+	-
Facial palsy	+	0	0	0	0
Loss of taste (anterior 2/3's)	+	0	+	+	-
Palatal paralysis	+	+	+	+	0
Hypesthesia pharynx	+	+	+	+	+
Paresthesias	+	+	+	+	+
Vasomotor paresis	+	0	+	0	0

## DISCUSSION

A comparison of the pathology involved in post-diphtheritic paralysis and Guillain-Barré's syndrome is made very confusing both by a paucity of literature covering the first disease and the probable multiplicity of diseases reported as Guillain-Barré's syndrome. Wilson<sup>10</sup> has perhaps more thoroughly covered the nervous system complications of diphtheria than any other recent observer. He has stated: "The naked eye changes in the nervous system are confined to the hemiplegic forms in which petechial bleeding or some focal effusions may be remarked or thrombosed vessels." Wilson has said that endotoxins of diphtheria act directly on and cause acute changes in certain cells of the neuraxis. They also act directly on peripheral nerves apart from the cellular origins of the latter. He summarizes the pathologic lesions as follows: "a. Motoneurons and sensory protoneurons are damaged by a neurotoxin acting directly on parenchyma, and that while in general nerve fibers suffer first and most, other cases are distinguished by a primary attack on either nerve cells or motor end organs; b. Aside therefrom

any part of the neurons concerned will exhibit secondary reactions according to the rules of degeneration. Under the microscope, the dominant lesion is seen to be a neuritis, a parenchymatous degeneration of myelin sheaths of both motor and sensory fibers through their extent." Norris and his group<sup>11</sup> reported one case coming to autopsy which showed severe degenerative changes in the medulla and anterior horns of the spinal cord pointing to definite central nervous system involvement as well as peripheral damage.

The pathology of Guillain-Barré's syndrome is equally vague. It was Guillain-Barré's original contention that their patients had only the most favorable prognoses. Since the original description, a number of fatal cases have been reported. It is not at all clear how many varieties of disease might be represented in these reported pathological studies. Baker<sup>5</sup> has reported two fatal cases with pathological findings. He found changes consisting of perivascular foci of demyelination scattered throughout the cerebral hemispheres, neuronal alterations within the cranial nerve nuclei, and patchy areas of myelin destruction within the peripheral nerves. Sabin and Aring<sup>12</sup> have reported three fatal cases with very careful and complete anatomical pathological studies. They found extensive visceral lesions consisting of focal degeneration and infiltration with mononuclear cells in the adrenals, liver and kidneys. Lesions in the heart consisted of interstitial infiltration with mononuclear and polymorphonuclear cells and, in one case, of necrosis of isolated muscle fibers and focal phlebitis. Zonal chromatolysis is described in the nerve cells of the spinal cord and medulla. In addition, degenerative changes were observed consisting of vacuolization and the appearance of many sharply outlined acidophilic bodies in the cytoplasm of some of the nerve cells in the abdominal sympathetic ganglia. After the study of these three cases, the writers expressed the belief that the existing data fit best the "hypothesis that infectious polyneuritis is caused by a toxin or toxins with affinities for the peripheral nerves and the viscera and elaborated by the microorganisms responsible for the infection of the respiratory tract which usually precedes the onset of nervous symptoms."

A comparative analysis of the clinical and clinico-pathological picture in post-diphtheritic paralysis and Guillain-Barré's syndrome is likewise not clear cut for the reader but less complex than that of the pathology. Case 4 which we have presented fits rather completely the classical signs, symptoms and clinical pathology of post-diphtheritic paralysis. There is the history of a sore throat with a membrane present and positive bacteriological findings clinching the diagnosis of diphtheria. The patient did not receive the known specific therapy until the ninth day of his illness, giving ample opportunity for the toxin to fix itself firmly in the nervous system tissue. After a delay of five weeks of comparative freedom from symptoms, there developed first ocular palsies, then palatal paralysis, to be followed soon by peripheral paresthesias, a gradual loss of all except superficial sensation and then a profound diminution in motor function. All of these signs and symp-



toms gradually disappeared over a period of weeks with a return to the normal. The spinal fluid findings were characteristically those of albuminocytologic dissociation.

The clinical picture of Guillain-Barré's syndrome has been elaborated by Baker's<sup>5</sup> study in which he reported 33 patients. He has emphasized the following characteristics of this syndrome referred to as a "disease": 1. Sudden onset, occasionally preceded by a history of antecedent infection of the respiratory passages. 2. Absence of those findings suggestive of a septic or toxic reaction in spite of severe clinical symptoms. 3. Cell protein dissociation of the spinal fluid. 4. Radicular involvement. 5. Facial nerve palsy. 6. Absence of mental symptoms. 7. Favorable prognosis. This conforms very well with the original criteria of Guillain-Barré with some modification.

Elevation of the spinal fluid protein in post-diphtheritic paralysis has been observed and noted by Wilson,<sup>10</sup> Baker<sup>5</sup> and others, but the albuminocytologic dissociation has not been emphasized. Since this has grown to be the most characteristic feature of the Guillain-Barré's syndrome, it is little wonder that so many cases are arbitrarily cited as examples with the finality of making a complete diagnosis. Ederle<sup>9</sup> has mentioned this finding in diphtheritic polyneuritis. He suggested that this placed it in the same category with "polyneuritis," "polyradiculomyelitis," Guillain-Barré's syndrome, etc. He further suggested this entire group be designated by the general descriptive term "serous radiculoneuromyelitis."

The above depicts the difficulty any student may have in attempting to compare either the clinical or the pathological findings in diphtheria of the nervous system and any other symptom complex at present falling into the group with which it is classified. This is especially true when it is noted time after time in case reports that the patient either shortly prior to the onset of neurological symptoms, or remotely so, had a respiratory infection or a sore throat.

Again referring to Wilson,<sup>10</sup> we find that he has recorded the frequency of neurological complications in diphtheria as varying with the observer from 8 to 66 per cent. Some variability of this incidence can also be attributed to the individual epidemic. The usual frequency is considered to be about 10 per cent. Norris et al.<sup>11</sup> report 18 cases of diphtheria occurring in the South Pacific 13 of which developed post infectious paralysis. This represents a very high incidence of paralysis, but is no doubt accounted for by the mild initial signs of infection and the late observation of the patients. Many cases showing mild ocular palsies and involvement of pharyngeal muscles surely go unobserved so that the exact incidence of nervous system damage is made still more difficult to determine.

The question naturally arises as to whether or not the five cases of polyneuritis observed here might have some unusual predisposition or susceptibility to nervous system damage by diphtheria toxin. This possibility was considered but not held likely. All patients had endured exposure, privation and additional disease. Four had been on inadequate diets for

weeks. Deficient vitamin intake was to be expected. Shulack and Peters<sup>13</sup> have recently reported a case showing spinal cord changes due to avitaminosis. The possibility of this patient having diphtheria previous to observation can not be dismissed. Failure to administer antitoxin early is apparently the important factor. Norris<sup>11</sup> and his associates found that antitoxin administered within four to 28 days of the onset of diphtheria did not prevent the paralysis. However, in those cases receiving antitoxin within three days, paralysis did not develop. This further confirms the belief that diphtheria toxin becomes fixed in nervous system tissue early after which it cannot be neutralized. In case 2 reported here, the patient received antitoxin five days after the onset of his illness. It did not prevent paralysis. Cases 1 and 4 received their antitoxin at much longer intervals after the initial appearance of diphtheria, hence no response was to be expected.

Cutaneous diphtheria as manifested by cases 1 and 5 is in itself of more than passing interest in war time. Cameron and Muir<sup>14</sup> have studied a group of 66 cases occurring in the Middle East. Saffron<sup>15</sup> has likewise reported such a case of recent date and reviewed the literature. Of particular import is the fact that Cameron and Muir found 12 cases of paralysis in the group of 66 cases observed. Unless the lesions are seen, examined, and an accurate bacteriologic examination made the true nature of the infection will go unrecognized. The broad areola of brown pigmentation surrounding the site of the original lesion we believe characteristic. It has color characteristics very similar to the residual pigmentation seen following a strongly positive Shick test. Two patients not included in this series but presenting signs of polyneuritis with elevated spinal fluid proteins had numerous lesions of like appearance on both legs. To us the diagnosis seems clear, but the lesions were healed and no bacteriologic examination could be made, hence they are not reported. The possibility that the resultant paralysis was improperly diagnosed as simple infective neuronitis or Guillain-Barré's syndrome is highly likely. *C. diphtheriae* finds cutaneous lesions and wounds excellent sites for remaining undetected until its toxin has attacked nervous system tissue.

#### SUMMARY

1. Five cases of post-diphtheritic polyneuritis ("serous radiculoneuro-myelitis") are presented.
2. A brief review of the literature covering the clinical picture, pathologic lesions and clinical pathology of the symptom complex variously known as "infective polyneuritis," "infectious polyneuronitis," Guillain-Barré's syndrome, has been made.
3. It seems probable that many cases reported as Guillain-Barré's syndrome, etc., are in reality cases of unrecognized diphtheria with late diffuse nervous system involvement.
4. Diphtheria should remain in the clinician's mind as a dangerous disease capable of high mortality if not recognized.

5. Cutaneous diphtheria is a serious lesion often resulting in prolonged disability because the toxin producing *C. diphtheriae* too frequently remains unrecognized while producing bizarre neurologic disease. The heavy areola of brown pigmentation surrounding the site of infection for months after healing is highly suggestive of a previous diphtheritic infection.

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## TOXIC REACTIONS ACCOMPANYING SECOND COURSES OF SULFONAMIDES IN PATIENTS DEVELOPING TOXIC REACTIONS DURING A PREVIOUS COURSE \*

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THE sulfonamide drugs are so commonly administered at the present time that practically every person has received one of them on some occasion. Consequently, it is of importance to consider what will happen when these individuals receive sulfonamides a second time. Lyons and Balberor<sup>1</sup> reported that in patients who received a course of sulfathiazole without exhibiting any toxic effects "drug fever" was more likely to develop during a second course of sulfathiazole than in patients receiving an initial course of this drug. Two of us<sup>2</sup> have shown that this principle also holds for other sulfonamides, and, furthermore, that when patients are given a second course of a sulfonamide drug different from the one administered previously, the incidence of toxic reactions will be no greater than in patients receiving these drugs for the first time.

Of equal importance is the question of what can be expected to happen to the patient who receives a second course of a sulfonamide when a febrile reaction has occurred during the first course. In the present paper, we have analyzed the data on all the adult patients coming under our observation who have received more than one course of the sulfonamide drugs and who developed fever, dermatitis, conjunctivitis, or any combination of these reactions during the first course. We have grouped all three of these toxic phenomena together because it is the general consensus that they are all due to the same underlying mechanism, and because these various reactions often occurred interchangeably during different courses of sulfonamides, as we will show later.

*Results.* There were 78 adult patients altogether who developed fever, dermatitis, or conjunctivitis, or a combination of these reactions during the first course of sulfonamide therapy, and who received a second course of sulfonamides. As shown in table 1, the same sulfonamide was administered during both courses to 48 patients. Thirty-three, or 69 per cent, of these patients developed one of the toxic reactions under discussion during the second course. Thirty patients received a sulfonamide for the second course different from that given the first time. Only five (17 per cent) of these patients developed a toxic reaction. These differences are statistically significant.

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† Capt. Lepper's contribution to this study was made before he entered military service.



The particular sulfonamide drug used during the first or second course seemed to make no difference. The three drugs most frequently administered during two courses, sulfathiazole, sulfadiazine and sulfamerazine, produced toxic reactions during the second course in 69, 70, and 69 per cent, respectively, of the patients to whom they were administered.

It is also of interest that there was no significant difference in the frequency of reactions observed during the second course, when the reaction occurring in the initial course was composed of fever or dermatitis alone, as compared with the frequency of reactions observed when more than one toxic reaction was manifested during the first course. For instance, when fever was the sole toxic manifestation during the first course, a toxic reaction developed during the second course in 14 (78 per cent) of 18 patients receiving the same sulfonamide during both courses, and in one (17 per cent) of six patients receiving another sulfonamide during the second course. It will be seen that these percentages are very similar to those found for the entire series.

TABLE II

Type of Toxic Reaction Developing during Subsequent Courses of Sulfonamides Compared to the Type of Reaction Developing during the First Course

Toxic Reaction during First Course	Toxic Reactions during Second and Third Courses						Total
	Fever	Dermatitis	Conjunctivitis	Fever and Dermatitis	Fever and Conjunctivitis	Dermatitis and Conjunctivitis	
Fever	16	0	0	3	0	0	27
Dermatitis	1	5	1	0	0	0	
Conjunctivitis	0	0	1	0	0	0	
Fever and Dermatitis	5	0	0	7	0	1	16
Fever and Conjunctivitis	3	0	0	0	0	0	
						32	11

In table 2 the types of toxic manifestations observed during the first course are compared with those observed during subsequent courses of sulfonamides. In general, the reaction tended to be the same during both courses, 29 patients showing the same reaction or combination of reactions, and 14 showing a different reaction or combination of reactions. Multiple reactions tended to occur more often during the first course (16 patients) than during subsequent courses (11 patients), but the differences were not statistically significant.

The length of the interval elapsing between the first and second courses had no bearing on the presence or absence of toxic reactions in the second course. In the case of one patient, fever began on the first day of the second course even though four months had elapsed between the courses of the sulfonamides. On the other hand, numerous patients failed to develop a toxic reaction during a second course, even though it began within a week after the end of the first course.

Nine patients received a third course of a sulfonamide after they had exhibited toxic manifestations to two previous courses of the same drug. In five of these patients, the third course produced toxic reactions. One of these five patients showed toxic reactions of increasing severity during the three courses, exhibiting fever with the first course, fever and pruritus with the second, and fever and a pruritic dermatitis with the third. Another one of the five patients, on the contrary, had fever and conjunctivitis during the first course, fever alone during the second, and only a low-grade fever during the third course. In another patient, similar phenomena of apparent desensitization appeared. This patient received only two courses of sulfadiazine and had fever and dermatitis both times. During the second course, however, the sulfadiazine was inadvertently continued after the appearance of the rash and fever, and these manifestations disappeared completely while the patient was still receiving the drug.

All of our attempts to prevent toxic reactions from recurring were unsuccessful. The measures which we used were: ascorbic acid, given between and during courses; aspirin or phenacetin, given just before and during courses; and small doses of the sulfonamide drugs themselves, given in one course lasting several days, or in several short courses.

### DISCUSSION

Park<sup>3</sup> tested nine patients who had developed fever, rash, or both, from the oral administration of a sulfonamide compound. All nine of them gave a similar reaction to a second course of the same drug whereas only three developed these toxic symptoms when given one of the other sulfonamides. It is apparent from his results and ours that the administration of a second course of a sulfonamide to a patient who developed fever, dermatitis or conjunctivitis during the first course of the same drug, is attended by a greater risk of toxic reactions. The risk is lessened considerably if a different sulfonamide is administered during each course, but it is still greater than we would expect in a patient who had experienced no toxic reaction to the first course. This can be shown by comparing the results obtained in the present study with those reported by two of us<sup>2</sup> on patients receiving second courses of sulfonamides, as we have done in table 3. This comparison also shows that the incidence of toxic reactions is less when a different sulfonamide is given than when the same sulfonamide is administered for both courses, whether a toxic reaction occurred during the first course or not. The present study, therefore, confirms the principle stated before,<sup>2</sup> that when a second course of sulfonamides must be given, the patient should receive a different sulfonamide from the one administered the first time.

Our findings also confirm the generally-held opinion that, in most instances, sensitivity to the sulfonamides is relatively specific for the individual drug, but that in some cases, a group sensitivity develops which includes several or all of the sulfonamide drugs.

TABLE III

Frequency of Drug Fever, Dermatitis and/or Conjunctivitis during First or Second Courses of Sulfonamides

Reaction to First Course	Sulfonamides Administered during Second Course	Total of Patients	Patients Developing Toxic Reactions during Second Course	
			Number	Per Cent
No	Different drug	169	6	3.6
No	Same drug	144	16	11.1
Yes	Different drug	30	5	16.7
Yes	Same drug	48	33	68.8
	(Control series of persons receiving one course only)	737	37	5.0

## SUMMARY AND CONCLUSIONS

1. Seventy-eight patients received a second course of a sulfonamide drug after showing fever, dermatitis or conjunctivitis during the first course. Among 48 patients to whom the same sulfonamide was given during both courses, 33, or 69 per cent, developed toxic manifestations, while only five, or 17 per cent, experienced a toxic reaction among the 30 patients who received a different sulfonamide during the two courses.

2. Neither the number of toxic reactions developing during the first course nor the particular sulfonamide drugs administered, nor the intervals elapsing between the two courses had any effect upon the appearance of toxic reactions during the second course.

3. Third courses were given to nine patients who had manifested toxic reactions to the first two courses of the same sulfonamide. Only five of these patients developed a toxic manifestation.

4. It is concluded that the patient who has previously experienced fever, dermatitis or conjunctivitis when receiving one of the sulfonamide drugs will run more risk of a similar reaction during a subsequent period of treatment with any of the sulfonamide drugs, even though a considerable interval of time may have elapsed between courses. If such a patient must be given a sulfonamide again, he should receive a different drug from the one used during the first course, and should be observed carefully for toxic reactions.

We wish to thank Dr. Lewis K. Sweet and the members of the Georgetown and George Washington Medical Divisions for their coöperation.

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# APATHETICAL RESPONSE TO HYPERTHYROIDISM; REPORT OF TWO CASES\*

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THE problem of differential diagnosis, treatment, and prognosis of the various manifestations of thyroid disease remains a puzzling one in spite of intensive study directed toward its solution. Enumeration of but a few of the many conditions which may be simulated follows. First, the classic Graves' disease must be distinguished from the ophthalmopathic type of Means.<sup>9</sup> In this latter condition an extreme degree of exophthalmos is the outstanding symptom, set in a background of relatively mild toxicity, and treatment in the form of thyroidectomy tends to increase rather than to correct the deformity. Second, an intrathoracic goiter may be confused with a mediastinal Hodgkin's or other neoplasm.<sup>3</sup> Here roentgen examination and biopsy of an appropriate gland may aid in determining whether or not operation is indicated. Hypothyroidism and the pituitary type of myxedema<sup>10</sup> may be indistinguishable without the aid of laboratory tests. The hypercholesteremia, increased serum proteins, and menorrhagia, typical in the former and absent in the latter, help determine the proper medication. The administration of thyroid alone not only is ineffective but may precipitate an adverse reaction in those with pituitary dysfunction. Not the least of these problems is the distinction between hyperthyroidism and certain functional nervous disorders, since such factors as emotional instability, fatigability, palpitation, and loss of weight may exemplify both groups. It is only by familiarity with the typical picture of thyroid toxicity, so aptly described in the eighteenth century by Parry, that we may be alert to its unusual manifestations. Diagnostic confusion is particularly apt to arise among older individuals in whom the presenting symptoms may be auricular fibrillation and cardiac decompensation; a thyrocardiac or cardiotoxic state must be distinguished from a purely organic cardiac disease. As far back as 1923 this relationship was pointed out by Hamilton<sup>2</sup> in his report of a series of 22 cases treated at the Lahey Clinic. These individuals had in common an enlarged heart, auricular fibrillation, congestive heart failure, and increased basal metabolic rates; they were all treated surgically with good results. Subsequently many such instances have been described<sup>1, 4, 5, 6, 7, 8</sup> wherein the clinical evidence of profound cardiac disturbance, usually in women past middle age, overshadowed the hidden factor of hyperthyroidism. The onset is typically gradual, the gland is firm and equivocally enlarged, the spectacular symptoms of toxicity may be wholly or in part replaced by a deceptive mask of mental and physical inertia.

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The cases to be reviewed suggest an even more exaggerated state of muscular weakness, apathy, and debilitation, yet at the same time are devoid of the cardiac manifestations.

#### CASE REPORTS

*Case 1.* M. M., a 55 year old housewife, was admitted to the Robert Long Hospital on September 19, 1944, because of choking spells, pain in the lower extremities, loss of appetite, and prostration. For two years her usual activities had been curtailed by dyspnea, palpitation, and emotional instability. Anorexia and weight loss developed proportionately, and more recently her ankles had been swelling in the evenings. Finally she had become bedfast two days before hospitalization.

**Physical Examination:** The patient was poorly nourished, weighing just less than 100 pounds, lay quietly in bed, and evinced no interest in her surroundings. There was no dissipation of energies, no expression of alacrity in her eyes. She was too weak to change her position in bed without help and the mere exertion of talking was accomplished with apparent effort. Her skin, particularly pigmented about the eyes, was soft in texture, warm, and moist. The temperature was 99° F., pulse 100, and regular. Blood pressure was 145 mm. Hg systolic and 70 mm. diastolic. A moderately enlarged, firm, nodular goiter was palpated. The precordium was active and the heart normal in size. A systolic murmur and an accentuated pulmonic second sound were present. The lung bases were clear and there was no peripheral edema.

**Laboratory Data:** Urine analysis gave a normal result. The hemoglobin content of the blood was 13 gm., and the white cell count was 5,000 with a normal differential. The Mazzini serologic reaction was negative. The sedimentation rate (Wintrobe) was 28 mm. in one hour and the blood non-protein nitrogen was 33 mg. per cent. Basal metabolic rates were +76, +50 and +54.

**Course in the Hospital:** She was treated with bed rest, vitamin B complex, and thiouracil 0.2 gm. three times daily. She was unable to feed herself the first few days but as her appetite improved she made gratifying though erratic progress; within a month her intake averaged above 2400 calories and she began to gain weight after an initial loss of four pounds. Her white count was checked regularly and at no time fell below the normal value. By the latter part of October she had become increasingly more stable, her basal metabolic rate was +24, and she was referred to surgery on the last day of October for a bilateral subtotal thyroidectomy. She was discharged from the hospital on November 8 following a satisfactory postoperative course.

**Pathological report:** Degenerating nodular goiter showing calcification.

A follow-up check on her condition five months and seven months later revealed a weight gain and increase in strength so that she was able to do her housework with ease. There was no residuum of her previous apathy.

*Case 2.* L. M., a 42 year old housewife, was sent to our hospital on September 17, 1942 with a tentative diagnosis of malignancy of the stomach, suggested by her complaints of inability to eat because of nausea and epigastric discomfort, malnutrition, and extreme weakness. She had begun to lose weight three years previously, at which time she weighed 189 pounds, but her local doctor was not consulted until April, 1942. She became bedfast in June because of nausea and vomiting and pain in her stomach and upon further questioning it was learned she had suffered severe financial reverses about this time. There was no record of hematemesis or melena but she had had recurrent episodes of diarrhea. In July she became jaundiced and had remained so. Her loss of weight and strength to the point of cachexia became alarming during the late summer. Nothing in her past history threw light on her present illness; she was the mother of eight children and had passed through an artificial postoperative menopause 13 years previously.

Physical examination revealed an emaciated individual weighing about 70 pounds. The temperature was 99.6° F., pulse 130, and blood pressure 150 mm. Hg systolic and 95 mm. diastolic. Her demeanor was that of utter lassitude and resignation, entirely devoid of every vestige of spontaneous animation. This mask was found to be vulnerable, however, to any references made to her financial losses, the apparent precipitating factor in her change for the worse early in the summer. To recall this to her mind was to initiate paroxysms of insuppressible weeping. Her skin had an icteric tint, was soft and warm, but showed evidence of dehydration. There was a minimal bilateral nodular enlargement of the thyroid. The heart size was not increased, the beats were regular and thrusting in nature, and a systolic murmur could be heard at the apex and along the left sternal border. Examination of the lungs was essentially normal. Palpation of the upper abdomen revealed tenderness and a questionable small epigastric mass. The liver border could be readily felt.

Laboratory Data: The urine was negative except for a faint trace of albumin. The white cell count of the blood was 7,600 with a normal differential. Hemoglobin was 13 gm., and Mazzini reaction was negative. Blood chemistry: direct van den Bergh positive; indirect 1.4 mg. of bilirubin; icteric index 29; serum cholesterol 165 mg. per cent; and non-protein nitrogen 25 mg. per cent. A glucose tolerance test was essentially normal and three basal metabolic rates were + 95, + 100 and + 100. Roentgen examinations of the chest, gall-bladder, stomach, and bowel revealed no demonstrable deformity.

Course in the Hospital: She was placed on a high caloric diet, vitamin B complex, and Lugol's solution, 10 drops three times a day. In spite of bed rest her pulse continued to fluctuate between 90 and 130. During the ensuing weeks her appetite and food tolerance increased so that she was averaging between 3900 and 4900 calories per day and her weight rose to 96 pounds. It was decided to operate upon her in two stages and accordingly the right lobe was removed on November 6. She returned the latter part of December for removal of the other lobe on January 6, 1943.

Pathological report: Partially involuted exophthalmic type of goiter with a few areas of nodular formation.

She was seen again in our out-patient department two years later in apparent excellent health. She weighed 171 pounds, had a good appetite, was working hard, and made no complaints.

### SUMMARY

These cases exemplify yet another clinical response to thyroid toxicity. A distressing picture of extreme apathy, disinterest, and resignation, associated with loss of weight and weakness to the point of prostration, made necessary a differential diagnosis from Simmonds' disease, advanced tuberculosis, Addisonianism, anorexia nervosa, and acute depressive psychosis. There was a profound masking of their fundamental problem of hyperthyroidism, but their satisfactory response to presurgical medical therapy, both in the form of Lugol's solution and thiouracil, and finally to thyroidectomy, corroborated the diagnoses.

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# SALICYLATE TOXICITY: THE PROBABLE MECHANISM OF ITS ACTION \*

By CHARLES M. CARAVATI, F.A.C.P., *Richmond, Va.*, and EDGAR F. COSGROVE, *Pittsburgh, Pa.*

FOR years it has been customary to administer alkalis in conjunction with oral salicylate therapy, based on the assumption that sodium bicarbonate protects the stomach by inhibiting the release of salicylic acid.<sup>1</sup> However, not until the recent work of Coburn<sup>2</sup> has it become customary to administer massive doses of salicylates over a protracted period. He advocates the intravenous and oral administration of sodium salicylate until a blood plasma level of over 300 gammas per c.c. is reached, and recommends that it be maintained at a high level for some weeks. In the application of this therapeutic procedure in our hands, in a comparatively small series of cases we were impressed that patients receiving salicylates intravenously experienced more nausea and vomiting than patients who received it orally. To establish clearly the mode of action of salicylate, a series of cases was analyzed and various studies performed and data assembled to determine the toxic action of salicylates particularly on the gastrointestinal tract.

1. *A Comparative Clinical Review.* A number of patients were given sodium salicylate by the intravenous route and blood level determinations made twice daily. A similar number were given equal doses of salicylate orally and salicylate levels determined twice daily. The level of salicylate in the peripheral blood was noted when nausea developed in each case in each group. Although it can be seen from table 1 that nausea and even vomiting

TABLE I  
Occurrence of Nausea during Salicylate Therapy

	Mean Plasma Salicylate Level (gammas per c.c.)	% Patients with Nausea
Group 1 Intravenous salicylate	372	58
Group 2 Oral salicylate	366	48

were experienced in both series, a larger number of patients who received the drug by the intravenous route experienced nausea than those to whom it was administered orally. Although it was demonstrated clearly that there was marked fluctuation in the blood level during the 24 hour period following the intravenous administration, and although higher peaks were reached than were possible by the oral route, more constant and stable levels were maintained by the latter method.

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2. *Simultaneous Administration of Sodium Bicarbonate and Sodium Salicylate.* Smull<sup>3</sup> and her co-workers have shown that the administration of sodium bicarbonate would promptly and materially reduce the serum salicylate level and that the simultaneous administration with salicylate drugs will prevent attaining a satisfactory elevated level. In the two groups of patients studied above, Group 1, receiving salicylates intravenously, and Group 2, receiving it orally, sodium bicarbonate was administered soon after nausea appeared. In each group, there was a prompt amelioration of the nausea, and within 12 hours there was no gastrointestinal dysfunction. Another study of the blood salicylate level in these cases after 24 hours showed that there was a marked and prompt reduction of the level that had been attained prior to giving the alkali, and that this reduction was about equal in both groups, as seen in table 2.

TABLE II  
Plasma Salicylates before and after Sodium Bicarbonate

	Mean Salicylic Level (Pre-Soda)	Mean Salicylic Level (24 hrs. after Soda)
Group 1 Intravenous salicylate	330	195
Group 2 Oral salicylate	295	188

3. *Urinary Excretion of Salicylates.* Although Smull et al.<sup>3</sup> emphasized that alkali should not be given simultaneously with salicylates as it prevented the attainment of a high blood level, they did not indicate the mechanism of this action. In the patients studied by us while administering sodium bicarbonate, quantitative urinary determinations for salicylic acid were performed. As can be seen from the table below (table 3), the administration of sodium bicarbonate will increase the urinary excretion of salicylate promptly, and in general, the higher the pH of urine, the greater the excre-

TABLE III  
Plasma and Urinary Salicyl before and after Alkali

Patients	Mean Plasma Level	Mean Plasma Level	Urine Salicyl	Urine Salicyl
	Pre-Soda	Post-Soda	Pre-Soda	Post-Soda
Case 1	320	184	444	595
Case 2	295	176	276	470
Case 3	392	264	470	523
Case 4	412	294	392	742
Case 5	304	192	260	448

tion of salicylates. Just as would be expected, there is a corresponding drop in the serum salicylate level as the urinary excretion increases. And further, by lowering the pH of the urine by the oral administration of ammonium chloride, the urinary excretion of salicylic acid is retarded and there occurs

a reciprocal increased concentration in the blood. In several cases after a relatively constant plasma salicylic level has been attained by the administering of a given quantity of salicylates, the administration of 3 to 8 grams of ammonium chloride orally would cause a prompt and sustained rise in the plasma level with a corresponding drop in the pH of the urine. The following case report illustrates these clinical and laboratory findings.

T. G., a white male, aged 23, was given 1.66 grams of sodium salicylate every four hours (a total of 10 grams daily) beginning three days after an attack of monocyclic rheumatic fever with fibrinous pericarditis. After three days of salicylate administration, the plasma level ranged from 260 to 280 gammas per c.c. At the same time the pH of the urine ranged from 6.3 to 6.6. At this time ammonium chloride, 4 grams daily, was given and within two days the plasma level rose to between 350 and 400 gammas and remained as long as the pH of the urine ranged from 4.7 to 5. Later, when ammonium chloride was discontinued and the urinary pH rose to 6.2, the plasma level dropped to 260 gammas per c.c.

4. *Gastric Secretion of Salicylate.* The favorable response from alkalis in the relief of the toxic symptoms from salicylates, administered either orally or intravenously, necessitated investigation to determine whether the effective relief was due to the prevention of local gastric reaction by the salicylates, or whether it may have been central in action. A group of cases was then studied, in which salicylates were administered intravenously until a high and fairly constant level was attained and tinnitus and nausea occurred, at which time gastric intubation was performed and the aspirated contents were analyzed quantitatively for titrable acidity and for the presence of salicylic acid in the stomach. In no case was there found any significant variation from the already determined basal acid secretion, nor was even a trace of salicylic acid found in the contents in any of the 15 consecutive cases in which the intubation was performed when the salicylic blood level was over 250 gammas per c.c. In several other patients a high level was attained by giving oral salicylate and from six to eight hours after the final oral dose was administered, gastric aspirations were performed and no evidence of salicylic acid was found in the contents removed from these stomachs. These convincing findings would seem to disprove the time-honored teaching that the nausea and vomiting experienced during salicylism are due to the presence of salicylic acid within the gastric lumen. Though salicylate permeates practically all body tissues and can be quantitatively measured in the saliva, spinal fluid, bile, synovial fluid, feces and urine, no trace of free salicylic acid has yet been found in the gastric contents of our patients receiving salicylates.

5. *Gastroscopy.* Twenty cases receiving salicylate therapy were gastroscoped in order to study the appearance of the stomach mucosa while toxic from salicylates.

Hurst and Lintott,<sup>4</sup> in 1939, reported hematemesis after the administration of aspirin and it has been quite uniformly accepted that salicylic acid and its compounds produce gastric irritation. For this reason, it has been cus-

tomary to advise against the oral consumption of aspirin in cases with peptic lesions or other gastric disturbances. These reactions are probably due to an unexplained hypersensitivity, and may occur after the ingestion of even a very small amount of the drug. William D. Paul<sup>5</sup> studied 228 cases before and after the oral administration of aspirin, and concluded that it did not cause irritation of the gastric mucosa in any cases studied by him. In 12 patients given intravenous salicylates, gastroscopic examinations were performed by us when the blood levels were over 300 and the patient was experiencing nausea or mild gastric unrest. Adequate visualization of the exposed gastric mucosa was accomplished in each case, and no evidence of any abnormality was seen in any case. Gastroscopic examinations were made in eight cases who had been receiving 12 grams of salicylates daily by mouth, two of whom were experiencing nausea at the time of the examination. No significant abnormalities of the gastric mucosa were observed in any of these cases except that one showed increased highlights and minimal superficial gastritis. These findings would indicate that no significant adverse effect upon the gastric mucosa results from either oral or parenteral salicylate therapy.

TABLE IV  
Gastroscopic Studies of Patients Receiving Salicylates

Method of Administration	Number of Patients	Number Showing Pathology
Intravenous	12	0
Oral	8	1

#### SUMMARY

1. Intravenous salicylates produce nausea, vomiting and dizziness as frequently as do oral salicylates.
2. Alkalis promptly reduce the blood level of salicylates by increasing urinary salicylate excretion.
3. Blood salicyl levels are dependent on size of the dose and the pH of the urine. The lower the urinary pH, the higher the plasma level of salicylates.
4. Salicylates are not found in gastric aspirates regardless of the height of the plasma levels.
5. Gastroscopy in 20 cases has failed to reveal any significant abnormal mucosal changes occurring during salicylism.

#### CONCLUSION

The data presented seem to indicate that the gastrointestinal symptoms noted during salicylate therapy are due to its action on the cerebral centers and not to any local effect on the alimentary tract.



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# THE PLASMA VOLUME IN LAENNEC'S CIRRHOSIS OF THE LIVER \*

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It has been previously observed that the increase in plasma volume, frequently encountered in patients with cardiac insufficiency, appears to be associated with right-sided failure.<sup>1</sup> The suggestion that this may be due to dilatation of the portal circulatory bed in response to elevation of the venous pressure has led to the present study. In order to determine a possible relationship between portal hypertension and the plasma volume, measurements were made in a group of patients with cirrhosis of the liver.

## MATERIAL AND METHODS

Ten patients with Laennec's cirrhosis were studied on the wards of the Presbyterian Hospital. The clinical diagnosis was confirmed by histologic examination (after surgery or post mortem) in three, and a presumptive diagnosis<sup>2</sup> was made in the remainder by a compatible history and physical examination, laboratory tests revealing abnormal liver function, and such evidence as hepatosplenomegaly, signs of collateral circulation, non-obstructive jaundice and ascites when present. Cases that were equivocal and those with diabetes or abnormal pigmentation were excluded from this series. Although edema was present in five patients, none gave a history or showed signs or symptoms of cardiac disease. The venous pressure was measured in five cases and was within normal limits.

In the presence of significant ascites, patients were weighed after paracentesis to minimize any error in the calculation of surface area, and these weights did not differ markedly from the average weight of the patient before the onset of cirrhosis. The cephalin flocculation test<sup>3</sup> was positive in varying degrees in all patients, and the bromsulfalein test was carried out on six patients by the injection of 5 mg. of dye per kilo of body weight. Blood samples for hematocrit and volume measurements were obtained with the patient lying flat in bed, and after at least a 20 minute period of inactivity in that position. The plasma volume was determined with the blue dye T. 1824, the optical density being measured with the photoelectric colorimeter.<sup>4</sup> Multiple serum samples were obtained 10 to 20 minutes after intravenous injection of the dye, predicted values being based on the data of Gibson and Evans<sup>5</sup> and the observed hematocrit. The difference between observed and predicted values was expressed as a percentage deviation from normal.

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TABLE I

## Clinical and Laboratory Data in 10 Patients with Cirrhosis

Case	Sex	Age	Weight kilos	Height cm.	Surface Area sq.m.	Liver —cm. below costal margin in mid- clavic. line	Spleno- megaly	Ascites	Collateral Circulation		RBC mill. per cu.mm.	Hema- tOCRIT per cent cells	Cephalin Floccu- lation	Brom- sulf. per cent retention in 30 mins.	Gm. per 100 c.c. serum		Pre- dicted Plasma Volume c.c.	Plasma Volume c.c.	Devia- tion from Pre- dicted Plasma Volume per cent
									Ab- normal Ab- dom- inal Veins	Eso- phageal varices					Alb.	Glob.			
1	M	48	74	177	1.91	3	0	0	0	0	4.9	48	++	20	3.2	3.0	2985	3240	+ 8
2	M	47	68	177	1.84	3	0	0	0	0	3.5	48	++		3.3	4.1	2860	2695	- 6
3	F	54	53	155	1.50	4	0	0	0	0	4.3	39	++		2.0	5.7	2380	2585	+ 9
4	M	52	58	162	1.65	4	+	+	+	0	3.5	47	++		2.5	5.1	2530	3065	+21
5	M	63	60	164	1.65	6	+	+	+	+	4.4	45	++	50	4.0	3.7	2625	2910	+11
6	M	64	70	170	1.81	0	+	+	+	0	4.9	40	++	35	2.9	2.0	3240	3825	+18
7	F	61	81	162	1.86	0	+	+	+	+	3.4	35	++	60	2.5	3.0	2730	3200	+17
8	F	52	61	160	1.63	11	+	+	+	+	3.8	37	++		3.8	3.1	2555	2845	+11
9	F	36	53	155	1.50	6	+	+	+	+	3.0	38	++	50	2.2	3.9	2420	3040	+25
10	M	34	64	181	1.82	0	+	+	+	+	3.7	41	++	15	2.8	3.4	3185	3835	+20

TABLE II

## Clinical and Laboratory Data in a Patient with Inferior Vena Cava Obstruction

11	M	37	84	180	2.04	6	+	+	+	+	13.0	4.6	42	0	5	2.5	3.5	3596	4520	+26
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## RESULTS

The results are shown in table 1. It is apparent that the majority exhibited an increased plasma volume, seven of 10 patients having values greater than 10 per cent above the predicted normal.

The three patients (cases 1-3), whose plasma volume fell within 10 per cent of the predicted values, showed no splenomegaly, abnormal abdominal veins or esophageal varices by barium roentgenographic studies, although one (case 3) had moderate ascites and edema in association with a serum albumin concentration of 2 gm. per 100 c.c. In the seven patients (cases 4-10) whose plasma volumes were greater than 10 per cent above the predicted values, abnormal veins or varices or both were invariably present, and the spleen was palpable in all but one. In one case a direct measurement of portal vein pressure was made at operation, an increase to 290 mm. of water being recorded.

The rise in plasma volume was unrelated to the degree of liver enlargement. The three patients without significant change in plasma volume all showed hepatomegaly, while no liver enlargement was demonstrated in three patients with plasma volume increases varying from 17 to 20 per cent above predicted values.

From the data it is also apparent that plasma volumes could not be correlated with the intensity of cephalin-cholesterol flocculation, degree of brom-sulfalein retention, or serum albumin and globulin concentrations.

## DISCUSSION

The increase in plasma volume in the majority of the cirrhotic patients studied cannot be explained by loss of dye in ascitic fluid. Examination of centrifuged ascitic fluid before and after dye injection in one patient with an elevated volume showed no change in colorimeter readings and similar conclusions have been reached by other observers.<sup>6</sup> Although delayed mixing was present in those with increased volumes, a constant disappearance slope following mixing gave no indication of any abnormal loss of dye from the circulation.

Some degree of anemia was present in many of this group. Gibson has reported an increase in plasma volume with some reduction in total blood volume in severe untreated pernicious anemia as well as reduction of red cell volume but with augmentation of blood hydration in the hypochromic anemias.<sup>7</sup> Although the observed increase in plasma volume might be in part attributable to anemia, the degree of hemoglobin and red cell reduction in the patients studied was not marked, hematocrit readings were essentially normal, and in some cases no significant anemia was present. Nor can hypoalbuminemia alone be responsible as a reduced plasma volume has been observed in such conditions as nephrosis and nutritional edema.<sup>8</sup>

It is a common clinical observation that patients with Laennec's cirrhosis may exhibit a decrease in urinary output, and that at times the tendency to

fluid retention or to diuresis is unrelated to changes in serum albumin concentration. The presence of an antidiuretic substance in the urine of some patients with cirrhosis has been recently reported.<sup>9</sup>

There are several reasons supporting the hypothesis that the observed increase in plasma volume may be related to portal hypertension and the secondary development of collateral venous circulation. In this series elevated volumes were regularly found in association with abnormal abdominal veins and esophageal varices. At operation or post mortem the number and caliber of collateral veins containing blood under increased pressure is often impressive. Measurement of abdominal vein diameters in several of these cirrhotic patients from infra-red photographs taken in the upright position, point toward a cross-sectional area much larger than that of the portal vein.

As added confirmation that venous obstruction results in a larger vascular bed, volume studies were carried out in a patient with obstruction of the inferior vena cava (table 2). A plasma volume 26 per cent above the predicted normal was recorded. This patient, a man of 37, developed leg varicosities, edema, and ascites over a period of several years after an upper thigh laceration. Examination also showed numerous large collateral veins over the abdomen and lower thorax, hepatosplenomegaly without laboratory evidence of significant parenchymal liver damage, hematuria and albuminuria, with a normal blood pressure and negative cardiac findings. Venous pressures were normal in the upper extremities, but markedly elevated ( $\pm 200$  mm. of water) in leg and femoral veins. There was no anemia.

The usual persistence of signs of portal hypertension after the development of a collateral circulation in cirrhosis is an indication that such an accessory venous bed does not completely replace that interfered with by the obstruction. Slow filling of compressed abdominal veins as well as circulation time measurements confirm the reduced velocity of blood flow in these collateral vessels. Other factors being equal, an increased sectional area would be required to carry this blood as a result of the reduced velocity. It would seem probable, therefore, that the increased plasma volume is due largely to such factors as distention of veins behind the point of obstruction and the increased sectional area required to handle the portal circulation in the face of a reduced velocity. It may be suggested that the increase in plasma volume is a reflection of the degree of development of the collateral circulation.

Lastly, it is of interest that the increase in plasma volume observed in the majority of cirrhotic patients studied is not as great as that found in right-sided cardiac insufficiency. In the former group the liver is scarred and possesses an impaired circulation, whereas in the latter the degree of liver engorgement may contribute a considerable increment to the plasma volume.

## CONCLUSIONS

1. The plasma volume was determined in 10 patients with Laennec's cirrhosis of the liver, an increase of more than 10 per cent above predicted values being found in seven patients.

2. An increased plasma volume was also recorded in a patient with obstruction of the inferior vena cava.

3. It is suggested that the chief factors responsible for the elevated plasma volume are the distention behind the point of portal obstruction and the increased size of the collateral vascular bed required to handle the portal circulation.

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# SERIAL PROTHROMBIN ESTIMATIONS IN CARDIAC PATIENTS: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS; USE OF DICUMAROL \*

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VENOUS thrombosis with pulmonary embolism has long been recognized as an important and serious complication in postoperative surgical patients. The significance of thromboembolism in medical patients and particularly in those with heart disease is only beginning to gain adequate recognition. Pathological studies<sup>1, 2</sup> have shown pulmonary embolism to be the main or contributory cause of death in one-fourth to one-third of patients dying with coronary occlusion or congestive heart failure.

White<sup>3</sup> has recently summarized the significance of thromboembolism in heart disease. Pulmonary embolism may simulate heart disease, especially myocardial infarction; it may precipitate a severe anginal attack or even myocardial infarction in a patient with coronary disease. It may complicate heart disease, especially congestive failure and myocardial infarction, and lead to a fatal outcome in a patient who would otherwise be expected to recover. Not infrequently, massive pulmonary embolism with sudden death may occur.

Through a series of careful pathological investigations by Rössle, Neumann, Frykholm and Hunter, et al.<sup>4</sup> it has been demonstrated that the source of most pulmonary emboli is in bland thrombi which originate in the smaller veins of the leg and propagate upwards. Venous thrombosis was found to occur more frequently in patients in the older age groups, in those with heart disease and in those confined to bed.

The recognition of the relation of venous thrombosis and pulmonary embolism to bed rest has stimulated the recent discussions regarding the dangers of bed rest.<sup>5, 6</sup> There has been little investigation of changes in blood constituents in cardiac patients which might influence the occurrence of thrombosis. To contribute information regarding this aspect of the problem, we have undertaken a careful study of one element of the clotting process, the prothrombin activity of the blood, in a group of patients with heart disease, including acute myocardial infarction and congestive failure. This type of data should be of especial interest since the introduction of the newer modes of anticoagulant therapy, heparin and dicumarol † has opened new possibilities for prophylaxis and treatment.

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† "Dicumarol" is the registered collective trade-mark adopted by the Wisconsin Alumni Research Foundation for the synthetic preparation 3, 3'-methylenebis (4-hydroxycoumarin).

## METHODS AND MATERIAL

A total of 76 individuals was studied. Thirty-two patients had evident cardiac disease, and in these, from two to 27 prothrombin determinations were done, with the exception of four cases in which only one determination was available. Nine non-cardiac patients with thrombo-embolism or thrombophlebitis were also followed by means of serial prothrombin times.

The control group of cases included healthy hospital workers and patients with various diseases whose nutritional status and physical condition were good. There were 35 individuals, 15 of whom were in the younger age group (between 20 and 39 years), and 20 of whom were in the older age group (between 40 and 81 years). The age distribution of the latter group was similar to that of the cardiac patients studied. In the control group, one determination was done in each of 15 cases, and from two to eight determinations in each of the remaining 20.

In the patients studied, serial prothrombin estimations were made from one to six times a week, and most cases were followed for two weeks or more, one case being studied for over three months. None of the patients received salicylates during the period of study, and vitamin K preparations and dicumarol were not given except in a few cases specifically studied. All of the patients in this series were under our close observation, and we have done or personally supervised all of the prothrombin determinations.

The method of prothrombin assay used in this study is based on the single-stage quantitative estimation described by Quick, Stanley-Brown and Bancroft<sup>7</sup> with the modifications introduced by Link and co-workers<sup>8</sup> and Shapiro.<sup>9</sup> Thromboplastin was prepared from rabbit lung by the vacuum desiccation method. The technic and apparatus involved in the determination have recently been clearly described by Shapiro.<sup>10</sup>

The method used follows in detail. To 0.5 c.c. of a 0.1 molar sodium oxalate solution are added 4.5 c.c. of blood obtained by venepuncture. The blood is centrifuged at 1700 r.p.m. for four minutes, and the plasma removed. Diluted plasma (12.5 per cent) is obtained by adding 0.1 c.c. of plasma to 0.7 c.c. of 0.85 per cent sodium chloride solution. The thromboplastin solution is prepared by adding 5 c.c. of saline to 100 mg. of the dried powdered rabbit lung, and the mixture stirred and heated at 56° C. in a water bath for 10 minutes, for extraction and in order to destroy prothrombin activity. The suspension is then cooled and .5 c.c. of a 0.025 molar solution of calcium chloride added, and the mixture centrifuged at 1700 r.p.m. for four minutes. The supernatant solution is removed for use. Whole and diluted plasma samples are placed in a rack in a constant temperature water bath (37.5° C.). Into 10 by 75 mm. test tubes, 0.2 c.c. of the thromboplastin-calcium chloride solution is transferred, and these tubes are also placed in the rack. The clotting times are determined after six minutes, when the contents of the tubes have reached bath temperature. Using a 0.1 c.c. micro blood sugar pipette, 0.1 c.c. of whole plasma is rapidly blown into a tube



containing the thromboplastin-calcium chloride solution, and the stop-watch, operated by a pedal, is started. A platinum wire stirrer with a loop at the end is moved slowly back and forth across the test tube until the end-point is reached, when the watch is stopped. The end-point for whole plasma is taken as the instant when the clot begins to move with the loop. The same procedure is repeated, using diluted plasma,\* the end-point here being the moment when the whole clot can be lifted as a unit, which occurs from one to several seconds after the clot first begins to form. Duplicate determinations were done in most cases.

## RESULTS

*Normal Values of Prothrombin Time.* 1. Control Series. These data include the 35 individuals previously described, and are given in table 1. The averages and standard deviations shown are calculated from the average of the serial determinations for each individual. The averages, divided according to age and sex, are also noted.

TABLE I  
Control Series

	Number of Cases	Whole Plasma Prothrombin Time (sec.)		12.5% Diluted Plasma Prothrombin Time (sec.)	
		Average	Standard Deviation	Average	Standard Deviation
Total group	35	17.8	$\pm 2.0$	45.2	$\pm 5.0$
Older age group (40-81 yrs.)	20	18.5	$\pm 2.0$	45.2	$\pm 5.0$
Younger age group (20-39 yrs.)	15	16.9	1.4	45.3	4.5
Older age group					
Males	12	18.7		46.1	
Females	8	18.0		44.0	
Younger age group					
Males	8	17.5		45.9	
Females	7	16.0		43.1	
Total (males)	20	18.3		46.0	
Total (females)	15	17.1		43.6	

2. Influence of vitamin K on prothrombin time of normals. Five normal individuals with diluted plasma prothrombin times well above the normal limits previously described for this method† were given large doses of preparations with high vitamin K activity, in order to observe whether the time could be shortened. None of these individuals had any evidence of liver disease. The results are noted in table 2.

\* The term "diluted plasma," unless further qualified, refers to the dilution of 1:8 or 12.5 per cent.

† The normal standards obtained by Shapiro<sup>10</sup> with rabbit lung thromboplastin and employing an identical method are as follows: Whole plasma, 15.5 seconds with a standard deviation of  $\pm 1.5$  seconds; diluted plasma (12.5 per cent), 39.5 seconds, standard deviation  $\pm 2.5$  seconds.

TABLE II  
Effect of Vitamin K on Prothrombin Time in Normal Individuals

Case No.	Average Prothrombin Time before Medication (seconds)		Menadione Bisulfite Total Dose (Mg.)	Duration of Medication (Days)	Average Prothrombin Time after Medication (seconds)	
	Whole Plasma	Diluted Plasma			Whole Plasma	Diluted Plasma
1	16	47	50	11	17	48
2	16	48	12	3	18	52
3	16	56	24	8	17	58
4	18	44	50	5	17	41
5	17	48	50	4	17	46

*Individual Variation of Prothrombin Time.* The average and standard deviation, and the range of the prothrombin time in serial determinations for each of seven individuals are shown in table 3. These include normal individuals and those with heart disease, but none received medication.

TABLE III  
Individual Variation in Prothrombin Time \*

Case No.	Number of Determinations	Prothrombin Time (seconds)			
		Whole Plasma		Diluted (12.5%) Plasma	
		Average and Standard Deviation	Range	Average and Standard Deviation	Range
1	13	17.3 $\pm$ 1.6	15-21	48.2 $\pm$ 2.5	44-54
2	15	17.5 $\pm$ 1.4	15-20	38.7 $\pm$ 2.2	36-43
3	14	18.9 $\pm$ 2.0	16-22	43.4 $\pm$ 2.4	35-50
4	14	18.5 $\pm$ 2.5	15-23	38.5 $\pm$ 2.6	31-45
5	8	18.3 $\pm$ 1.3	16-21	44.4 $\pm$ 2.6	40-48
6	8	16.3 $\pm$ 1.3	14-17	57.3 $\pm$ 2.7	53-62
7	8	17.3 $\pm$ 1.1	16-19	42.6 $\pm$ 3.3	40-48

\* This series includes normal individuals and patients with heart disease.

*Effect of Digitalis on Prothrombin Time.* The results are given in table 4. Digitalization was effected rapidly (within 24 hours) or over a period of days, and maintenance dosage continued. The total period of digitalis medication is noted.

In addition, there were 11 cases who had been taking maintenance doses of digitalis for periods of two weeks to many months before admission. The average prothrombin time in this group was 18.8 seconds (whole plasma) and 47.9 seconds (diluted plasma).

The average prothrombin time of all 18 cases who received digitalis was 19.0 seconds (whole plasma) and 47.5 seconds (diluted plasma).

One patient received 3.6 gm. digitalis leaf in four days and developed toxic signs but there was no change in prothrombin time.

*Effect of Bed Rest and Ambulation on Prothrombin Time.* Fourteen patients were studied who were confined to bed for varying periods of time,

TABLE IV  
Effect of Digitalis on Prothrombin Time in Cardiac Patients

Case No.	Prothrombin Time before Digitalis (seconds)		Prothrombin Time after Digitalization (seconds)		Duration of Digitalis Medication (days)
	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma	
1*	18	47	18	47	12
2	18	41	19	43	2
3	19	36	18	36	3
4	16	44	17	42	1
5	20	44	19	46	2
6	20	59	23	60	11
7	21	54	20	52	8

\* This patient developed toxic manifestations after receiving 3.6 gm. of digitalis leaf in four days.

from seven to 52 days. In 10 of these, prothrombin determinations were available at the onset of bed rest or shortly thereafter, during the course of bed rest and at its termination, and also after several days or more of ambulation. The data are given in table 5.

TABLE V  
Effect of Bed Rest and Ambulation on Prothrombin Time in Cardiac Patients

Case No.	Duration of Bed Rest (days)	At Onset of Bed Rest*		Average Prothrombin Time (seconds)			
				At End of Bed Rest		After Ambulation†	
		Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma
1	25	18	39	17	37	17	40
2	31	21	44	19	44	17	41
3	30	19	41	18	38	19	41
4	23	19	43	18	47	17	45
5	12	16	36	17	38	18	33
6	52	18	39	18	47	16	47
7	7	20	43	19	45	18	44
8	14	21	47	21	52	15	45
9	14	18	42	19	46		
10	26			21	68	20	65
11	15			17	47	18	48
12	10	20	59	23	58	23	60
13	12	23	60	20	52		
14	7	18	47	17	46	18	50

\* First determinations were made within one to five days after onset of bed rest except in one case.

† Determinations were made after three days or more of ambulation.

*Prothrombin Time in Congestive Heart Failure.* A total of 20 patients is included, in which serial prothrombin determinations were done in the presence of failure. The average prothrombin time for each case, and the averages for the groups are noted and classified according to the degree of failure (table 6).

TABLE VI  
Prothrombin Time in Congestive Heart Failure

Degree of Failure*	Mild*		Moderate*		Advanced*	
Number of cases	7		11		2	
	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma
	(seconds)		(seconds)		(seconds)	
Average prothrombin time of all cases in each group:	18	43	19	50	18	47

\* Degree of failure represents the extent at the time of prothrombin estimation.

Mild degree: slight venous distention, liver at or just below costal margin, 0 to 1+ edema.

Moderate degree: moderate venous distention, liver 2 to 4 cm. below costal margin and tender, 1 to 2+ pitting edema.

Advanced degree: marked venous distention, hydrothorax, liver below umbilicus and tender, 3 to 4+ pitting edema.

*Prothrombin Time in Recovery from Congestive Failure.* Nine individual cases were followed with serial prothrombin times during the course of recovery from congestive failure. Only patients with moderate or advanced degrees of decompensation who showed marked improvement during observation were included. The findings are presented in table 7.

TABLE VII  
Prothrombin Time in Recovery from Congestive Failure \*  
Average Prothrombin Time (seconds)

Case No.	During Congestive Failure		After Recovery	
	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma
1	21	44	19	45
2	19	41	18	39
3	16	36	17	36
4	20	44	19	45
5	21	47	15	45
6	24	58	16	47
7	18	42	20	45
8	20	59	23	60
9	21	55	20	52

\* All patients included in this group had moderate or advanced degrees of congestive failure which improved markedly or cleared completely during observation. All received digitalis.

*Prothrombin Time in Coronary Occlusion.* Five patients with acute coronary occlusion were studied. The initial estimation was obtained five days after onset in two cases and between 11 and 24 days after onset in three. The average time of the five cases was 19.8 seconds (whole plasma) and 43.4 seconds (diluted plasma). The shortest diluted plasma time was 39 seconds (in two cases) and the longest time was 50 seconds.

*Prothrombin Time in Angina Pectoris.* Five patients were studied during the course of repeated attacks of angina pectoris. The overall average

of the mean times for each was 18.2 seconds (whole plasma) and 45.9 seconds (diluted plasma). On one occasion, in one of the patients, a severe anginal attack was coincident with an abnormal acceleration of the diluted plasma prothrombin time to 34 seconds, with no change in whole plasma time.

*Prothrombin Time in Mural Thrombosis with Embolism.* Two patients were observed in whom myocardial infarction was followed in several weeks by arterial embolism, indicating the presence of left ventricular mural embolism. Prothrombin study was begun a few days after embolism. The average times in the first case were 18 seconds (whole plasma) and 41 seconds (diluted plasma). In the second case the times were 23 seconds and 39 seconds respectively. Three patients were observed who had rheumatic heart disease, auricular fibrillation and multiple embolism (pulmonary and systemic) indicating auricular thrombi. One case showed an average prothrombin time of 21 seconds (whole plasma) and 60 seconds (diluted plasma). The other two patients were treated with dicumarol before adequate base values were obtained, but the marked reaction to dicumarol exhibited in both indicated that there was no increase in prothrombin activity.

*Prothrombin Time in Thrombo-embolism and Thrombophlebitis.* A total of eight cardiac patients with pulmonary embolism and infarction was studied by means of serial prothrombin estimations. Four of the patients showed no deviation from the normal prothrombin time; three patients showed a slight, relative shortening of diluted plasma time in comparison with the usual (or normal) value for each individual; only one patient showed a definite abnormal shortening of the diluted plasma prothrombin time (34 seconds) and this was three days after operation.

There were five non-cardiac patients studied who showed thrombo-embolism. These included three postoperative patients, one pregnant patient at term, and one with thrombophlebitis and pulmonary embolism. Four of these cases showed an abnormal acceleration of diluted plasma prothrombin times taken one to three days after the occurrence of embolism, the times being from 29 to 34 seconds (diluted plasma). In the fifth patient the time was 42 seconds (diluted plasma). The whole plasma times were normal.

Four patients were observed who had thrombophlebitis of the leg veins without embolism; one of these was a cardiac patient. In only one of the group (a non-cardiac patient) was an abnormal acceleration of the diluted plasma time observed (33 seconds); in the other cases, the times were within normal limits.

In the course of the entire study, apart from the cases cited above, an abnormal acceleration of diluted plasma prothrombin time was encountered on only three occasions: in one case, without evident cause; in a second instance occurring two weeks later in the same patient there was a simultaneous occurrence of a severe attack of chest pain which may have represented a pulmonary embolus; in the third case the diagnosis was pneumonia,

but pulmonary infarction could not be excluded. The diluted plasma prothrombin times in these three instances were between 31 and 33 seconds.

*Administration of Dicumarol to Cardiac Patients.* Six cardiac patients were given dicumarol therapeutically. All of these patients had evidence of embolism. The dosages and responses are briefly summarized.

1. A patient with arteriosclerotic heart disease and pulmonary infarction received 1.0 gm. of dicumarol in 10 days, with subsequent rise of whole plasma prothrombin time to 65 seconds.

2. A patient with rheumatic heart disease and auricular thrombosis with embolism received 1.0 gm. of dicumarol in 16 days, with rise of whole plasma prothrombin time to 80 seconds.

3. A patient with rheumatic heart disease, auricular thrombosis with multiple embolism who was critically ill, showed a rise of whole plasma prothrombin time to 48 seconds three days after a single dose of 300 mg. of dicumarol, with slow return to normal values over the period of a week.

4. A patient with arteriosclerotic heart disease developed pulmonary embolism three days postoperatively showed an abnormally accelerated diluted plasma prothrombin time (34 seconds). He was given 500 mg. of dicumarol in two days and three days later showed a rise in whole plasma prothrombin time to 170 seconds, with bleeding from the operative wound. He was given a 500 c.c. fresh blood transfusion and 100 mg. of an active vitamin K preparation (menadione bisulfite) in the next three days. Following the transfusion, there was an immediate cessation of bleeding, and the prothrombin time fell to normal levels and was maintained. The subsequent administration of 100 mg. of dicumarol produced no change in prothrombin time. The patient was critically ill in the first week following pulmonary embolism, but he subsequently made a fairly rapid recovery.

5. A patient with acute myocardial infarction and suggestive signs of pulmonary embolism was given 600 mg. of dicumarol in seven days, with rise of whole plasma prothrombin time to 75 seconds.

6. A patient with rheumatic heart disease, thrombophlebitis and pulmonary infarction received 350 mg. of dicumarol in five days, with rise of whole plasma prothrombin time to 40 seconds.

## DISCUSSION

*Validity of Method of Prothrombin Estimation.* The method of prothrombin estimation used in this study is based on the single-stage quantitative estimation first described by Quick, Stanley-Brown and Bancroft.<sup>7</sup> Link and his associates<sup>8</sup> and Shapiro<sup>10</sup> have introduced certain modifications which have increased the value and accuracy of the method. Estimation of prothrombin time with diluted plasma enables the detection of small changes in prothrombin activity which would not be evident with whole plasma. The explanation for this resides in the relation between the concentration of prothrombin to the clotting time. In the higher concentration range of prothrombin, wide variations in prothrombin concentration cause

relatively slight changes in the clotting time, whereas in the concentration range below 25 per cent even small variations in prothrombin concentration result in marked changes in the clotting time (Quick<sup>11</sup>). In addition, the naturally occurring anticoagulants present in blood in varying activity are rendered largely ineffective by plasma dilution (Link<sup>8</sup>). The dilution of 1:8 (12.5 per cent) has been found most useful in studies on human patients (Shapiro,<sup>9, 10</sup> Brambel and Loker<sup>12</sup>).

*The Normal Values of Prothrombin Time.* It is necessary to ascertain the normal values for the prothrombin time and the normal range of variability for the individual and group before the significance of observed changes under certain experimental conditions can be properly interpreted. Reports from various laboratories show that the normal value may be different for each laboratory, and the "normal" for the whole plasma prothrombin time has been reported in the range between 10 and 25 seconds. In this study, rabbit lung thromboplastin prepared by the vacuum desiccation method was used because of its high degree of consistency. The technic outlined by Shapiro<sup>10</sup> was followed in detail. Our control values show some difference from his results. The normal standards reported for the method by Shapiro are: 15.5 seconds, standard deviation 1.5 seconds for whole plasma; 39.5 seconds, deviation 2.5 seconds (12.5 per cent) diluted plasma. Our control figures are: 17.8 seconds, deviation 2.0 seconds (whole plasma); 45.2 seconds, deviation 5.0 seconds (diluted plasma). The lack of effect of vitamin K on the clotting times of some of the control cases indicates that the higher values obtained by us were not due to dietary deficiency and were probably normal values. The greater standard deviation which we found necessitates more caution in the interpretation of slight deviations from the normal. It should be noted that the individual variability in prothrombin times was found to be considerably less than the group variability. Slight changes in the serial prothrombin times of any one individual, especially if consistent, may have significance. No significant age or sex difference was found.

*Effect of Digitalis on Prothrombin Activity.* There have been few reports on the effect of digitalis on the coagulation mechanism, although it would be important to determine whether the widespread use of this drug influences the formation of thrombi. Werch,<sup>13</sup> Macht<sup>14</sup> and de Takats, et al.<sup>15</sup> reported work on animals indicating that digitalis preparations increase the coagulability of the blood. Massie and co-workers<sup>16</sup> reported work which indicated that digitalis given in therapeutic doses to human patients results in a shortening of the whole blood coagulation time but has no effect on prothrombin time as measured by the Smith bedside test.

Our results do not demonstrate any effect of digitalis on the prothrombin time of whole or diluted plasma, whether the digitalis is given for short, or long periods, whether digitalization is effected rapidly or slowly, and even if a toxic dose is given.

There is no clear evidence up to the present time that therapeutic doses

of digitalis in human patients increase the coagulability of the blood or the tendency to thrombosis, and digitalis should not be withheld because of such fears, where it is indicated. The statistics of Williams and Rainey<sup>2</sup> indicate that the control of congestive failure reduces the incidence of leg vein thrombosis.

*Effect of Bed Rest and Ambulation on Prothrombin Activity.* There is much evidence, previously noted,<sup>4</sup> that prolonged bed rest greatly increases the incidence of venous thrombosis and pulmonary embolism. The recent discussions of the dangers of bed rest have emphasized this problem.<sup>5,6</sup> The reasons for this increased incidence are not fully understood, although the mechanical factors involved seem to be fairly evident. According to our data, there is no evidence that bed rest or ambulation, per se, has any effect on the prothrombin activity of the blood. When thrombophlebitis or thromboembolism occurs, however, the prothrombin time may change in some cases, as will be discussed more fully below. It should be emphasized that thrombosis and embolism not infrequently occur in patients who have not been confined to bed. This has been noted by other authors<sup>17,18</sup> and we have encountered it as well.

*Prothrombin Activity in Congestive Heart Failure.* The liver has been shown to be the main site of prothrombin production.<sup>19</sup> Since the plasma prothrombin level is affected by liver function, it might be expected that the hepatic congestion occurring in cardiac decompensation would result in an appreciable reduction in prothrombin activity. Previous work<sup>20</sup> has demonstrated some impairment of liver function in right heart failure. On the other hand, the high incidence of thrombo-embolism in congestive failure might have some relation to an increase in prothrombin activity.

The prothrombin activity in congestive heart failure, as measured by the whole and diluted plasma prothrombin times in our group of patients, showed no significant change in either direction. The average prothrombin times of patients with various degrees of failure showed little difference, and the serial prothrombin times of individuals recovering from failure showed no significant change. The average prothrombin time of all of the patients with cardiac decompensation was not different from the normal values of the control series.

*Prothrombin Activity in Thrombo-Embolism.* Shapiro and his associates, in a series of papers,<sup>9,10,21,22</sup> have presented evidence of an increase in prothrombin activity occurring in acute thrombophlebitis and thromboembolism. In these cases, they found an acceleration of the diluted plasma prothrombin time beyond the normal limits, while the whole plasma time was normal or prolonged. Shapiro, Sherwin and Gordimer<sup>21</sup> found that increased prothrombin activity, in the form of an accelerated diluted plasma prothrombin time, was present in the majority of postoperative patients, occurring in the second week following operation. In a few cases, a marked increase in prothrombin activity was noted to precede the occurrence of pulmonary embolism by several days. Brambel and Loker obtained similar



results in postoperative patients and patients with phlebitis. The only other condition in which an abnormally short diluted plasma prothrombin time has been consistently reported is parturition.<sup>23</sup> At the present time, the evidence indicates that any acceleration of diluted plasma prothrombin time beyond the normal limits does not occur under normal circumstances.

The data previously reported have been based on studies of surgical and obstetrical patients almost entirely. In our investigation of eight cardiac patients with thrombo-embolism, followed by means of serial prothrombin determinations, the characteristic abnormal acceleration of the diluted plasma prothrombin time was seen in only one, and in this patient it was also three days after operation. Four patients showed no change, but three gave indication of a relative acceleration of the diluted plasma time; however, this could be established only by prior or subsequent determinations to ascertain the normal level for the particular patient. In contrast, four of five non-cardiac patients who developed venous thrombosis and pulmonary embolism showed the characteristic acceleration of the diluted plasma prothrombin time, in confirmation of the previous work cited.

The difference in the findings between the cardiac and non-cardiac groups of patients is of interest. The significance of an abnormally shortened diluted plasma prothrombin time is not definitely known. It may represent an increased prothrombin concentration or activity (hyperprothrombinemia) or it may be related to factors, other than prothrombin, which are affected by dilution, such as anticoagulants, protein fractions, or other unknown quantities. Shapiro<sup>10</sup> feels that it represents a true hyperprothrombinemia, which is not reflected in the whole plasma prothrombin time because of the presence of interfering anticoagulant substances. The absence of response (increased prothrombin in the presence of thrombosis) in the cardiac patients we have studied, may be related to an inability to produce excess prothrombin or it may reflect other changes in the plasma protein fractions of the cardiac cases. Shapiro<sup>24</sup> has reported an abnormal acceleration of diluted plasma prothrombin time in a case of multiple myeloma with a markedly elevated serum globulin, indicating that a change in the protein fractions of the blood may affect the prothrombin time as measured independently of the actual prothrombin concentration. It is true that our cardiac patients had complications such as congestive failure, myocardial infarction or bronchopneumonia, and were in general in poorer physical condition than the postoperative and postpartum group who were otherwise healthy individuals.

The significance of an accelerated diluted plasma prothrombin time in relation to intravascular thrombosis is difficult to determine. This finding may precede the occurrence of recognizable venous thrombosis or pulmonary embolism by several days, but it frequently is coincident with thrombo-embolism or appears a few days subsequently. If the increased prothrombin activity is presumed to be a causal factor in thrombosis, the latter observation is difficult to explain. Furthermore, it is not apparent in what way an ac-

celeration of prothrombin conversion by a few seconds could influence the occurrence of intravascular thrombosis. Warner et al.<sup>25</sup> have demonstrated a more rapid conversion of prothrombin in dogs and other animals though thrombosis is not more frequent. Shapiro<sup>10</sup> has noted that in cases of arterial embolism or thrombosis there is no shortening of the diluted plasma prothrombin time. No changes in prothrombin time were observed in our cases of coronary thrombosis, peripheral arterial embolism and thrombosis, or mural thrombosis of the cardiac chambers. The acceleration of the diluted plasma prothrombin time seen in cases of venous thrombosis may be an effect rather than a cause of the thrombosis, in that there may be an absorption of circulating anticoagulants at the site of thrombus formation. The antithrombin activity of the blood has been shown to decrease markedly during the process of clotting.<sup>26</sup> Diminution of anticoagulant activity would be reflected in an acceleration of prothrombin time more readily in the diluted plasma, where any remaining anticoagulant activity would be destroyed in the process of dilution. The absence of such an acceleration of prothrombin time in arterial thrombosis might then be due to the fact that venous thrombosis is usually much more extensive.

*Relation of Pulmonary Embolism to Angina Pectoris and Myocardial Infarction.* There have been a number of reports of the effects of pulmonary embolism on the heart. Friedberg and Horn<sup>27</sup> in a postmortem study of 37 cases of myocardial infarction without coronary artery occlusion, found that the most frequent cause was pulmonary embolism. Horn, Dack and Friedberg<sup>28</sup> and Currens and Barnes<sup>29</sup> reported cases with anatomic changes in the myocardium following pulmonary embolism in the presence of well-marked coronary sclerosis. Pulmonary embolism probably produces these effects by causing shock and asphyxia, which result in myocardial changes and even acute infarction in the presence of coronary sclerosis and insufficiency. Schönbrunner<sup>29</sup> suggested that a reflex vagal response in pulmonary embolism produced coronary spasm and cited two cases in which angina pectoris occurred after embolism and was relieved by nitrites.

In our series, one patient had two attacks of myocardial infarction, probably preceded in the first, and clearly preceded in the second, by pulmonary embolism with pulmonary infarction. The last pulmonary infarct was preceded by evidence of increased prothrombin activity and by several repeated anginal attacks which were unusually severe, which may have been precipitated by small pulmonary emboli. Another patient showed an abnormally short diluted plasma prothrombin time coincidental with a severe attack of chest pain similar to angina pectoris. Here, again, a small pulmonary embolus may have occurred.

*Response to Dicumarol in Cardiac Patients.* The effect of dicumarol on the prothrombin time has been set forth in a series of papers<sup>30</sup> which have dealt mainly with surgical patients. The average dose recommended is 300 mg. of dicumarol for the initial dose and 200 mg. the next day, with subsequent dosage dependent on the prothrombin time, the therapeutic level being

about 35 seconds (whole plasma). Elevation to 50 seconds (whole plasma) or above was found to be dangerous, with the occurrence of hemorrhage a likely possibility. Dicumarol was used in relatively few patients in this study, but the difference of its effect in these cardiac patients was so marked that the results are being reported.

Our results indicate that a dose of 500 mg. of dicumarol even when spread over a period of five to seven days caused excessive and dangerous elevations in prothrombin time in the cardiac patients. It is striking that elevations up to 80 seconds (whole plasma) did not result in bleeding. Only one patient developed hemorrhage, from an operative wound, after the administration of 500 mg. of dicumarol in two days, resulting in a very severe depletion of prothrombin. This patient responded quickly to a fresh blood transfusion and large doses of vitamin K.

On the basis of these results, it is recommended that the dosage schedule of dicumarol be reduced in treating cardiac patients. An initial dose of 200 mg. is usually safe, and the prothrombin level should be determined two days later and daily thereafter. Dicumarol may then be given, 100 mg. each day if the prothrombin time is less than 35 seconds (whole plasma) and withheld if the time is in excess of this figure. If markedly elevated prothrombin times occur despite precautions, large doses of vitamin K preparations should be given intravenously (30 mg. three to four times a day) until the time is restored to normal levels. Cromer and Barker<sup>31</sup> have reported on the value of massive doses of vitamin K. Where actual hemorrhage occurs, an immediate fresh blood transfusion is also indicated.

*Indications for Dicumarol Therapy.* 1. Coronary Thrombosis. Although Solandt and Best<sup>32</sup> and Dale and Jaques<sup>33</sup> have shown that the anti-coagulants, heparin and dicumarol, can prevent intravascular thrombosis and specifically coronary thrombosis in experimental animals, the known pathological basis of coronary thrombosis in man and the relative infrequency of premonitory signs preclude any important use of these drugs in the prophylaxis of thrombosis of the coronary arteries.

2. Mural Thrombosis in Myocardial Infarction. The frequent occurrence of thrombosis overlying a myocardial infarct and the subsequent occurrence of severe and even fatal embolic episodes have been reported by a number of authors (reviewed by Blumer<sup>34</sup>). Blumer reports the overall incidence of mural thrombosis in myocardial infarction as 50 per cent. Solandt, Nassim and Best<sup>35</sup> have demonstrated experimentally that heparinization can prevent the development of mural thrombosis over an area of injured cardiac muscle. Furthermore, Mallory, White and Salcedo-Salgar<sup>36</sup> showed that mural thrombi do not form until the fifth day or later after infarction, and that organization of the thrombus is usually complete by the sixteenth day, being followed by the formation of a new endothelial lining. Moreover, they presented evidence that mural thrombosis is probably due to local dilatation at the site of the injured muscle and that the endothelium

almost always remains intact. This would indicate that a large infarct would be more likely to cause mural thrombosis.

In view of these considerations, it would seem valuable to administer dicumarol to patients developing myocardial infarction of a severe degree, such as would be most likely to develop large, friable mural thrombi. It is suggested that the drug be started as soon as possible after onset and continued for three weeks. The drug should be used only where facilities for doing accurate prothrombin times daily are available. The dosage schedule has been discussed. The interval of at least five days after myocardial infarction before mural thrombi begin to form allows adequate time for prothrombin depletion. The dicumarol therapy would have the added advantage of helping to prevent venous thrombosis during the initial period of required bed rest. This therapy is probably not as important in the case of the mild type of myocardial infarction, though occasionally there occurs peripheral embolism from mural thrombi following a "silent" coronary. We have begun this mode of therapy in a few cases, but a proper evaluation would require the compilation of results of treatment of a large number of cases.

3. Auricular Thrombi with Multiple Embolism. Embolism from auricular thrombi is a highly unpredictable occurrence and effects of therapy are difficult to evaluate. We have treated two cases without spectacular results. In a case with repeated, frequent embolism, dicumarol may be tried, since no other form of rational therapy is available, and it should then be given over a long period of time.

4. Thrombophlebitis, Venous Thrombosis and Pulmonary Embolism. There have been many reports on the value of dicumarol in the prevention and treatment of thrombophlebitis, bland thrombosis and embolism<sup>30, 22, 37</sup> and the evidence indicates that dicumarol can reduce the incidence of post-operative thrombo-embolism, prevent further embolism after it has occurred and lead to more rapid resolution of phlebothrombosis and thrombophlebitis. Our brief experience in the use of dicumarol in cardiac patients has been therapeutically satisfactory and we have not noted further embolism where the prothrombin time was adequately elevated. Dicumarol is indicated where there is clinical evidence of thrombosis or phlebitis, especially if embolism has occurred, and should be maintained for two to three weeks, with smaller doses for a longer time if possible. The patient may be allowed out of bed when the temperature is normal, provided that the prothrombin time is adequately elevated.

The question of the relative values of anticoagulant therapy and vein ligation in thrombo-embolism is undecided. Anticoagulant therapy prevents further thrombosis and probably hastens the healing of the formed thrombus; it also acts throughout the body. Vein ligation excludes the thrombus from the circulatory system, but it does not prevent thrombosis elsewhere and it is difficult to use where local signs are not present. Homans<sup>38</sup> has

presented an excellent discussion of vein ligation from the surgeon's standpoint. In the absence of conclusive evidence in either direction, it is suggested that dicumarol be used in the presence of thrombo-embolism, and that vein division be reserved for the infrequent cases which show recurrent embolism following institution of adequate therapy.

### SUMMARY AND CONCLUSIONS

1. The method of prothrombin estimation used in this study was found to be reliable and accurate. The normal values of the prothrombin time were found to be 17.8 seconds, standard deviation  $\pm 2.0$  seconds (whole plasma) and 45.2 seconds, standard deviation  $\pm 5.0$  seconds (12.5 per cent diluted plasma). The individual variation of diluted plasma prothrombin times was about half as great as the group variation. The normal values were not changed by administration of large doses of vitamin K.

2. No effect on the whole or diluted plasma prothrombin time was observed in a group of 18 cardiac patients who received digitalis for varying periods of time. A review of the literature revealed no definite evidence that digitalis administered to patients in therapeutic doses has the effect of promoting thrombosis or embolism. Digitalis should be used in heart failure where indicated, since the control of failure is a factor in the avoidance of thrombo-embolism.

3. Bed rest for periods up to seven weeks did not produce any change in prothrombin activity, except in a few cases in which a change was associated with the occurrence of thrombo-embolism. Ambulation did not affect prothrombin activity.

4. The presence of congestive heart failure did not influence prothrombin activity, nor was any change observed following recovery from failure.

5. In the cases of coronary occlusion, as well as those with repeated attacks of angina pectoris, there was no characteristic alteration in prothrombin activity. One case developed myocardial infarction following pulmonary infarction on two occasions; during one of these there was evidence of increased prothrombin activity. Two other cases had attacks of angina pectoris probably precipitated by small pulmonary emboli, and here there was indication of increased prothrombin activity at the time of the attacks.

6. In five patients who had mural thrombosis of the cardiac chambers with embolism, no specific change in prothrombin activity was noted.

7. Eight cardiac patients developed thrombophlebitis or thrombo-embolism. In four of these there was no alteration in prothrombin time; in one case, there was an abnormal acceleration of the diluted plasma prothrombin time; and the remaining four showed a slight relative shortening of the diluted plasma prothrombin time when compared with the patient's usual level, though the times remained within the normal range. This is in contrast to the findings observed in postoperative and postpartum patients with thrombo-embolism, in which most of the patients presented an abnormally accelerated diluted plasma prothrombin time.

8. There is little known of the relation of the prothrombin activity of the blood to the occurrence of intravascular thrombosis. There is no evidence that an increase in prothrombin activity leads to thrombosis, though a marked decrease in prothrombin, such as that produced by dicumarol, can completely prevent thrombosis. The abnormal acceleration of the diluted plasma prothrombin time which has been observed in cases of thrombo-embolism may be entirely secondary to the thrombosis. There is some indication that the accelerated time which has been interpreted as evidence of increased prothrombin concentration or activity, may be related to other factors, such as changes in the protein fractions of the blood.

9. Cardiac patients appear to be more sensitive to dicumarol than others. Cardiac patients with thrombo-embolism who were given an "averaged" dose of 500 mg. of dicumarol over a period of two or more days developed excessive and dangerous elevations of the prothrombin time. The administration of dicumarol to cardiac patients or any patients in a debilitated state must be done with caution. A tentative dosage schedule for cardiac patients is suggested.

10. The therapeutic indications for dicumarol have not been established. Thrombo-embolism in cardiac patients is such an important cause of morbidity and mortality that every measure of control should be used. Dicumarol appears to be indicated in the following groups of cardiac patients: those presenting evidence of phlebothrombosis, thrombophlebitis or venous thrombo-embolism; those confined to bed in whom successive prothrombin times reveal an acceleration of the diluted plasma time even if no definite signs of thrombosis are present. The results are questionable in patients with auricular thrombosis and multiple embolism. Dicumarol is probably of no value in preventing or minimizing coronary thrombosis, but it is suggested that it be used during the first three weeks following severe myocardial infarction, in an effort to prevent mural thrombosis and venous thrombosis. Dicumarol should never be used unless there are facilities for accurate daily estimation of prothrombin time.

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# THE POSTMORTEM EXAMINATION IN CASES OF SUSPECTED HOMICIDE \*

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THE postmortem examination in cases of suspected homicide represents one of the most important applications of medicolegal science to the needs of the community. Its proper performance is of paramount concern to those agencies of government responsible for law enforcement and the effective administration of justice. In view of the desire of the medical and legal professions, increasingly evident in recent years, to improve the standards and quality of medicolegal practice throughout the country, it was considered timely and appropriate again to review the subject of the postmortem examination in cases of homicide, and to point out what is expected in the way of performance of the person entrusted with it. In a paper published several years ago, the author described and discussed the routine procedures necessary in such examinations.<sup>1</sup>

## INADEQUACIES OF MEDICOLEGAL AGENCIES AND OF THE STATUTES PERTAINING TO THEM

At present, in most sections of the country, the postmortem investigation of homicide is inexpertly and inadequately carried out. The chief reasons for this unsatisfactory performance are to be found in the faulty organization of official medicolegal agencies responsible for such investigation and in the lack of uniformity of statute laws which have established such agencies, and defined and limited their functions. The deficiencies inherent in governmental medicolegal departments have discouraged able physicians from specializing in legal medicine, thus permitting the practice of such an important specialty to fall into the hands of untrained and unqualified medical persons. Legal medicine, as a specialized branch of medical science, has not kept pace with the progress made during recent years by the other specialties. There are only a few places in the country where it is practiced by trained specialists, and it is therefore not surprising that the postmortem examination in homicide cases is performed haphazardly and unsatisfactorily by untrained, and inexperienced physicians. As long as the inadequate medicolegal systems now in force throughout the country are permitted to

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In April 1943, the *Annals of Internal Medicine* published a series of articles dealing with subjects of joint interest to the medical and legal professions, as part of a symposium which was published in various medical and legal journals. This was prepared under the editorial supervision of Hubert Winston Smith, M.D., now Professor of Legal Medicine at the University of Illinois, Urbana, Ill. This article is one of a continuation of that series. An index of the entire series may be obtained from Dr. H. W. Smith at cost (20 cents).

continue, the unsuspected homicide will escape detection and the obvious one will be inexpertly and improperly handled medically.

An examination of the statute laws pertaining to coroners and to medical examiners in the United States <sup>2</sup> reveals that, in most jurisdictions where the office of coroner exists, and also in some of the comparatively few localities where there is a medical examiner's system, the statutes provide only for the investigation of obviously violent and suspicious deaths. There does not appear to be any recognition of or provision for the important fact, so well known in medicolegal experience, that in many violent deaths there are not any externally obvious or suspicious signs of violence on the body of the deceased. Since the statutes in most instances do not provide for the routine official investigation of such cases, certain unsuspected homicidal and other types of violent death, not outwardly obvious or suspicious, necessarily escape detection.

In two States, namely Massachusetts and Rhode Island, where there is a medical examiner's system, permission for a medicolegal autopsy, which the medical examiner deems necessary, must first be obtained from some other authority, usually the prosecuting attorney, who is in a position to refuse such permission or to question the necessity for the autopsy. In those jurisdictions where there is a coroner, that official, even though not a physician, can decide whether or not a postmortem examination is necessary.

#### DESIRABLE FEATURES OF MEDICAL EXAMINER'S SYSTEM IN NEW YORK CITY, ESSEX COUNTY (NEW JERSEY) AND NASSAU COUNTY (NEW YORK), AND THE STATE OF MARYLAND

The coroner's office in New York City was abolished and a medical examiner's office established in its place by an act of the State Legislature passed in 1915.<sup>3</sup> The law went into effect in 1918. A similar medical examiner's system was instituted in Essex County, New Jersey, which includes the City of Newark, in 1927, and in Nassau County, New York, in 1938, and in the entire state of Maryland in 1939, by statutes almost identical with that which created the medical examiner's office in New York City. In these four jurisdictions, the medical examiner's office functions entirely independently of other official agencies, and the responsibility for the entire medicolegal investigation rests with a trained medical personnel. The investigations of the medical examiners are in no way controlled or hindered by any other agency. In these four offices, the law <sup>4</sup> requires that all sudden, suspicious, unusual, and violent deaths, and deaths where there has not been any physician in attendance, must be reported to the medical examiner's office for investigation by a medical examiner, no matter how seemingly unsuspecting the death may be. It is only by the routine investigation of this great variety of deaths, that unsuspected homicides are discovered.

Other medicolegal systems concerned only with obviously violent and

suspicious deaths permit certain unsuspected, not obviously violent homicidal cases to pass undetected. This is a fundamental defect in the medicolegal systems of most jurisdictions in the United States. This defect cannot be corrected merely by improving the quality and training of the medical personnel, but it will continue until the statutes are altered to require the prompt investigation from the very beginning, by trained medical examiners, of all sudden and unusual as well as suspicious and violent deaths.

Lay persons, whether private citizens, police officers, prosecuting attorneys, coroners, or physicians not trained to carry out medicolegal investigations, cannot decide the nature of sudden death or of death where there has not been any medical attention, and they should not be burdened with that responsibility. Their opinion of any such death should not preclude an investigation by a medical examiner with the authority to decide upon the advisability and necessity of autopsy, and to perform such autopsy. The practice in most communities of referring only the obviously violent and suspicious cases to the medicolegal department for investigation is responsible for the too frequent embalming and burial of bodies, necessitating their subsequent exhumation for autopsy, because violence not being apparent was not suspected at the time of death. It follows that a certain number of cases of unsuspected homicide remain buried and are never discovered, and it is not an exaggeration to say that a subtle murder may go uninvestigated and undiscovered.

In New York City, of a total of about 75,000 deaths each year, from 15,000 to 16,000, or roughly 20 per cent, are referred to the Office of the Chief Medical Examiner for routine investigation<sup>5</sup> because of the medical examiner's law. Of the referred cases, about 5,000 or one-third are violent deaths, and of these, about 350 are homicidal. Thus, homicides constitute approximately 2 per cent of the total number of deaths investigated each year.

A number of violent deaths, including some which are homicidal, are detected each year only by careful routine postmortem investigation, the cases having first been reported to the Medical Examiner's Office as non-suspicious. Such cases would not have been investigated and autopsied and would have escaped detection in those jurisdictions where only obviously violent and suspicious deaths are reported to the authorities. If unsuspected violent deaths and homicides are to be detected, all sudden, unexpected and unusual deaths must be investigated routinely by an official medicolegal agency.

#### QUALIFICATIONS OF PHYSICIAN PERFORMING EXAMINATION

In every homicide and in every death where there is the slightest suspicion of homicide, a postmortem examination including a complete and accurate autopsy should be performed on the body of the deceased by a qualified and authorized physician. The person entrusted with this examination should be a pathologist trained in that branch of legal medicine called

*forensic pathology* and working in the official capacity of a medical examiner or coroner's physician. There should be adequate facilities at his disposal for the performance of an autopsy and for any other investigation along histological, chemical, bacteriological and serological lines which are indicated by the nature of the case. The fallacious idea exists in the minds of many of the laity and some of the medical profession that any physician, because of eminent qualification in some other branch of medicine, or any pathologist without medicolegal training, is qualified to carry out this special type of postmortem investigation.

#### CARELESS PERFORMANCE AND MISINTERPRETATION OF AUTOPSY

In many cases of homicide, the inadequate postmortem examination by an incompetent or unqualified physician has been followed by a grossly erroneous interpretation of the findings. Many homicidal deaths have escaped detection because of the failure on the part of an inexperienced and careless investigator to recognize the more subtle anatomic evidences of criminal violence.

In obvious cases of homicide, in which only superficial postmortem examinations were thought necessary, the lack of detailed medical information has seriously handicapped the work of law-enforcement agencies. Thus, the police have been deprived of valuable clues which the complete postmortem examination would have revealed, and they have been hampered in their attempts to solve the crime. In other instances where a perpetrator has been apprehended and brought to trial, the prosecuting attorney has found himself at a serious disadvantage because of the lack of complete medical evidence necessary for the proper establishment of the *corpus delicti*.

There have also been deaths from purely natural causes which because of the circumstances were misinterpreted and attributed to homicidal violence, with the subsequent prosecution and conviction of an accused innocent person for a non-existent crime. The failure to understand the anatomic findings in a postmortem examination, and their misinterpretation, have not infrequently resulted in flagrant miscarriages of justice. Thus, artefacts, some produced by the embalmer, also normal findings, natural disease processes and accidental and suicidal injuries have been erroneously considered evidence of homicidal violence.

The writer is aware of a case in which it was alleged that the deceased died after having been struck on the head with a slipper. After an incomplete autopsy limited to the head of the embalmed body, a medical opinion was arrived at and testified to that death had resulted from the blow to the head. The brief autopsy report did not disclose any pathologic changes in the skull or brain attributable to trauma. The cause of death was certainly not determined since the body was not opened nor was any chemical examination made of the brain for the presence of alcohol. This chemical test was precluded because the body had been embalmed before the incomplete autopsy

was performed. Nevertheless, the accused person was convicted of homicide which was not proved medically.

#### POSTMORTEM EXAMINATION COMMENCES AT SCENE

The scope of the postmortem examination in a frank or suspected case of homicide extends beyond the mere determination of the cause of death and the means by which it was brought about. In homicidal cases where the deceased is found dead, the postmortem examination properly commences with a careful study by the medical examiner of the undisturbed dead body at the place where it was discovered. This scene may or may not be the place where death occurred and it is not necessarily the place where the violence which caused the death was inflicted.

Thus, the undisturbed dead body of a woman was found on the sidewalk at 2 o'clock in the morning. The circumstances under which it was found and the examination of the body revealed that it had been dead for some time and moved after death. Rigor mortis had disappeared and there were postmortem lividities on the front of the body as well as on the back. Death had been caused by strangulation. The solution of this case is described on page 694 under the topical heading of Routine Blood Grouping Determinations.

In another case, the deceased was stabbed while on the street and then ran across the roadway, up two flights of stairs into his apartment where he locked himself in the bathroom and died. When examined by the police and the medical examiner, the undisturbed dead body was found seated on the toilet. The cause of death was a stab wound through the heart.

It is extremely important to learn the circumstances surrounding the death. Although it is true that in the majority of homicides, even a superficial postmortem examination will establish the homicidal nature of the death, there are certain types of homicide in which the evidences of violence are superficially lacking and it is only the careful study of the undisturbed body at the scene and the circumstances surrounding the case, which arouse suspicion that the death may be homicidal. Such a body removed from the scene may show nothing externally to suggest a violent death and thus might escape the close scrutiny and careful necropsy which would certainly be indicated if it were examined in its original surroundings by a trained medical observer. The practice required by law in the City of New York of having a medical examiner visit all dead bodies at the places where they are found has minimized the possibility of the unsuspected homicide passing unnoticed.

The types of homicide which may readily escape suspicion and detection if the scenes are not visited include deaths from manual and ligature strangulation, smothering, carbon monoxide poisoning, certain deaths caused by concealed stab wounds and bullet wounds and also some deaths from criminal abortion.

There are many cases in which a complete and careful necropsy indicates that death resulted from violence, but cannot establish that the death was necessarily by homicidal means. The necropsy findings in certain cases of drowning, carbon monoxide and other types of poisoning, blunt force injuries, especially those resulting from falls from a height, may be consistent with homicidal, suicidal or accidental death. Only a careful investigation of the circumstances surrounding the death will enable the medical examiner to classify the case correctly. The classification of a certain number of violent deaths must remain undetermined. This is especially true of drowning cases, in which the bodies are recovered after long periods of submersion, and cases of poisoning in which the clinical course was of long duration and the diagnosis unrecognized during life.

Experience with the many ordinary and bizarre forms of violent death is of the greatest value to the medical examiner in helping him decide the homicidal, suicidal or accidental nature of any given case. The experienced observer is quick to recognize the suicide which has been tampered with in the attempt to create the impression of a homicide, usually for purposes of collecting insurance, or the homicidal case which has been altered to make it resemble a suicidal, accidental or natural death.

#### EXAMPLES

Many examples<sup>6</sup> can be given to illustrate the importance of the examination of the body at the scene by the medical examiner in helping to determine the homicidal, suicidal or accidental nature of a violent death.

The body of a young negress was discovered at the foot of a long flight of stairs, lying on its back, the head resting on the first step, the legs sharply flexed under the thighs. The handle and part of the blade of a new, long, single-bladed jack knife were plainly visible protruding from a fatal stab wound of the chest. At necropsy, the point of the knife was found to have penetrated an intercostal space, the pericardium and the pulmonary artery, death having resulted from an intrapericardial hemorrhage.

The unusual position of the body and the weapon at first aroused the suspicion of homicide but investigation at the scene disclosed that the deceased had purchased the knife on the previous day, and that a short time before her death, had visited her estranged husband who was living in the apartment at the top of the stairs. After an unsuccessful attempt to effect a reconciliation, the deceased left the apartment in a depressed mental state mumbling something as she passed through the door. On the landing outside the door, she was seen to slump to her knees. The witness who saw this ran back into the apartment for help but when she returned to the landing, the deceased had already staggered or slid down the full length of the flight of steps to the place where her body was discovered. Her purse and several drops of blood were found on the tiled floor of the upper landing near the apartment door. The necropsy revealed that the track of the stab wound was a short one and could readily have been self-inflicted with the use of slight force. Needless to say, the husband and others in the apartment were subjected to a thorough questioning, and it was learned from them and from other reliable sources that the deceased had been despondent and had threatened suicide.

In another case a suicidal shooting at first had aroused suspicion of homicide. The body of the deceased scantily clad was found lying on the bed. There was a contact

bullet wound of entrance above the left breast, and a corresponding exit wound on the back of the left side of the chest. The bullet was found embedded in the wall behind the bed. A revolver was found near the edge of the bed under the right hand of the deceased, but it had evidently been tampered with after the shooting, by someone who removed the discharged cartridge shell from the cylinder chamber and substituted for it a single, undischarged cartridge. There was reason to believe that this had been done by the common-law husband who owned the pistol and who ignorantly believed that the substitution would remove any suspicion that he might have shot the deceased. Fortunately, the case was clarified by a suicide note in the deceased's handwriting.

In another case<sup>7</sup> investigated by Dr. Morgan Vance, the homicidal character of a smothering was suggested to him by the position of the undisturbed dead body of a young woman sprawled out in a prone position on the bed with the face buried in a pillow. There were no external or other evidences of injury, only the signs of asphyxia. The male companion of the victim was apprehended and confessed that he smothered her while trying to stifle her screams. If the medical examiner who performed the autopsy had not first examined the body at the scene the homicidal character of the death could not have been established nor would it have been suggested from the autopsy alone.

### PROCEDURE IN SUSPICIOUS DEATHS

When a dead body is discovered in New York City, and the indications definitely point to homicide or are suspicious of homicide, the police who are the first in authority to arrive at the scene, immediately notify the Office of the Chief Medical Examiner of the death and a medical examiner is promptly dispatched to the scene of the death. Such cases take precedence over non-suspicious deaths. In regard to the latter, it has already been emphasized that an apparently non-suspicious death may be homicidal. It therefore behooves the medical examiner to be on the alert in the investigation of every case if the unsuspected homicide is to be discovered.

There must be no delay in the visit of the medical examiner to the scene, no matter what time of the day or night the case is discovered. The body and its surroundings may not be disturbed until after the medical examiner has arrived and completed his preliminary investigation.

The preliminary examination by the medical examiner is carried out in coöperation with members of the Police Department including detectives especially trained for the investigation of homicidal cases. In addition to the experience which these detectives receive in the field, handling the many cases assigned to them, the New York City Police Academy for many years has conducted systematic courses for detectives in which they are taught the essentials of the medical indications of crime. These courses are given by members of the medical staff of the Office of the Chief Medical Examiner who utilize for the purpose a very extensive collection of lantern slides, illustrating actual cases of the ordinary and extraordinary types of homicidal, suicidal and accidental death. Significant details revealed by the study of the dead body at the scene are especially emphasized in these courses. Needless to say, this teaching has been enthusiastically received and has proved most valuable in bringing about an intelligent and sympathetic coöperation

between members of the Police Department and the medical examiners in their investigations of violent deaths.

#### INDEPENDENT CHARACTER OF MEDICAL EXAMINER'S INVESTIGATION

The medical examiner conducts his investigation independently of other law enforcement agencies. His functions do not fall under the jurisdiction of the police authorities or prosecuting agencies. Nevertheless, he coöperates fully with these other departments, informing them of the probable nature of the case, offering useful suggestions and supplying them with whatever information is revealed by his examination at the scene and by the subsequent necropsy. He should be entirely unbiased in his study of any case and must not venture any opinion which he cannot justify by the findings in his examination. He must bear in mind that he is an investigator and not a prosecutor and if his investigation clearly discloses that there are no medical indications of crime in a suspicious or a violent death, or that the findings are not necessarily indicative of homicidal violence, he must be prepared to give such an opinion. If the medical findings definitely point to criminality, the examiner must be firm in his opinion even though the outward appearance of the case at first did not suggest such a possibility.

#### STEPS IN INVESTIGATION AT SCENE

Upon his arrival at the scene of a suspicious or frankly homicidal death, the medical examiner records the time and place of his arrival and examination, and inquires into the circumstances under which the body was found. He determines how, when and by whom the body was first discovered and if possible by whom and when the deceased was last seen alive. He obtains the name and shield number of the first police officer, usually a patrolman, to arrive at the scene and a statement from him as to the time he was notified about the finding of the body, the name of the person who notified him and the time he first saw the body.

The medical examiner also inquires of the patrolman or of the first person who found the body as to its original position and whether or not the body had been moved from its original position after it was found. Such might be the case if the deceased was still alive or thought to have been alive when first discovered. Any attempts at resuscitation necessitating movement of the body, disarrangement of the clothing, the application of tourniquets, bandages or towels to bleeding wounds, should be recorded, also the name of any ambulance surgeon who might have treated or moved the deceased or pronounced him dead.

In cases where attempts at resuscitation have been made, the medical examiner should instruct the patrolman and the ambulance surgeon to record promptly and fully the original condition and position of the deceased when first seen by them. Frequently hospital surgeons called upon to treat wounded persons, have neglected to describe accurately the patient's wounds, omitting mention of their exact nature, number, size and location.



In many homicidal cases, not immediately fatal, the descriptions of the wounds in the hospital records are inadequate. It must be remembered that the original appearance of a fatal wound may be obliterated by a surgical operation, performed in the attempt to save the patient's life. Should the patient die later, the medical examiner may be unable to recognize and describe the characteristics of the original wound. This information can be furnished only by the surgeon who first saw and treated the patient. It is therefore important that every surgeon should be familiar with the detailed characteristics of penetrating and non-penetrating wounds, which might result from homicidal violence. There is a regrettable lack of interest and knowledge among many practising physicians and surgeons concerning the interpretation and recognition of the various types of bullet and stab wounds, lacerated wounds and blunt-force injuries which they may be called upon to treat, and about which they may be called later to testify in a criminal action. Through carelessness or ignorance, many important details of wounds are overlooked, details which may have considerable medicolegal importance in subsequent criminal proceedings.

#### IDENTIFICATION OF BODY BY POLICE OFFICER

The body of the deceased with its clothing is identified to the medical examiner by the first patrolman who saw it. If such identification is not made at the scene, the police officer must report to the mortuary and there identify the body and clothing to the medical examiner. The identification by the police officer is necessary in every homicidal case and especially in those cases in which the deceased did not die immediately but survived for a variable period of time in a hospital, for in such instances the medical examiner would not have seen the deceased at the scene of the crime. The police identification is an indispensable link in the chain of evidence necessary to connect the dead body, autopsied by the medical examiner, with the particular crime of which the perpetrator is accused.

The time and place of the police identification must be carefully recorded. It is not sufficient for the patrolman simply to come to the morgue and look at the dead body; he must identify it to the medical examiner or to some other available and responsible person who in turn will see or has seen the body in the presence of the medical examiner handling the case. Whenever possible, it is also advisable to have the identification made to any other medical examiners present at the autopsy. This identification to another medical examiner will enable him to testify to the autopsy findings and cause of death in the event of the enforced absence from the trial of the medical examiner who performed the autopsy.

#### PHOTOGRAPHING THE SCENE

Prior to the handling of the body and before disturbing any of the surroundings at the scene, as many photographs should be taken as are necessary

to show all the details. These photographs are best taken by a Police Department photographer equipped with a view camera having a wide-angle lens and capable of taking a fairly large size, usually an 8 by 10 inch, picture. Photo-flash bulbs are used as a source of illumination, permitting the photographs to be taken in any kind of light. The medical examiner may also take photographs and should make a diagrammatic sketch of the scene, indicating the size and shape of the room, the arrangement of the furniture, doors and windows and the position and location of the body, blood stains, weapons, discharged bullets and cartridge shells, also any other noteworthy findings.

### SIGNS OF DEATH

He then proceeds to an examination of the body, paying particular attention to the signs of death.<sup>8</sup> He carefully notes and records the extent of rigor mortis, the degree of cooling of the body and in this connection the amount of clothing or covering on the body and the temperature of the room. The color, location and amount of the postmortem suggillations or lividity and the presence of any other postmortem changes, such as putrefaction, mummification, adipocere formation, and destructive marks on the body, caused by insects, such as ants, and blowfly larvae, or by rodents and larger animals, should be noted; also any attempts at dismemberment and disposal of the body. Putrefactive changes and postmortem mutilations by animals should not be confused with antemortem wounds.

The careful study of the signs of death enables the trained investigator to form some estimate of the probable postmortem interval. Such estimates are the more accurate, the shorter the interval. At best, only a guarded opinion should be given concerning the postmortem interval, because the onset, progress and duration of rigor mortis and the rate of cooling of the dead body may show great variation, being dependent upon many factors.

The position of the body with reference to the location and color of the suggillations is of great importance in determining whether or not the body has been moved after death. In this connection, it must be realized that if the body is moved immediately after death, before the suggillations have appeared, such movement will not be detected by a study of the lividity when the body is found. Estimates as to the probable postmortem interval can only be made if the body is visited at the scene, and are impossible if it is examined for the first time on the following day, after it has been moved and chilled in the refrigerator over night. Reliable information as to the probable postmortem interval is of considerable value to the police in their investigations and in their attempts to trace the movements of the deceased prior to death, and to check any alibis which may be offered by a suspected perpetrator.

The color of the postmortem suggillations is significant to the trained medical observer in that it may reveal the cause of death. The cherry red

color of the lividity in carbon monoxide poisoning is easily recognized. It is also important not to mistake deep blue suggillations for antemortem bruises, an error which the inexperienced observer may make.

### PRELIMINARY EXAMINATION FOR WOUNDS

The body is then examined for obvious wounds but a final opinion as to their exact nature and number should not be ventured on the basis of this preliminary examination at the scene. The nature of many wounds is self-evident. In shooting cases, it is helpful to the police if, in addition to the entrance wounds, obvious exit wounds are found with corresponding holes of exit of bullets in the clothing. A search of the premises may then reveal a bullet. In some instances, a bullet, in passing through the body, may carry with it a strand of hair or a fragment of bone or soft tissue. At times, a bullet may be felt just beneath the skin and may be easily removed by a small skin incision. The character and calibre of such a bullet may show whether it was fired from a revolver or automatic pistol. If fired from the latter type of weapon, an ejected cartridge shell should be searched for and if found would indicate that the deceased had probably been shot at the place where the body was found.

The detailed examination of bullet and knife wounds is best made at the time of the necropsy, when the wounds can be carefully washed and studied. The presence of considerable extravasated blood may obscure their finer details at the scene. In assaults with blunt weapons, the pattern and extent of a wound may suggest the type of weapon that should be sought for by the police, but again the finer detail of the pattern will be more readily detected at the necropsy, after the surface of the wound is cleansed of blood and other material which may obscure it.

The hands of the deceased should be carefully examined for the presence of defense wounds, powder burns and residues, blood stains, various objects such as strands of cloth and hair and fragments under the finger nails.

### COLLECTION AND PRESERVATION OF EVIDENTIAL MATERIAL

It is the responsibility of the medical examiner to preserve all objects found on or in the body of the deceased, which may have anything to do with the cause of death, or which may furnish clues useful in the apprehension and conviction of the assailant. Thus, the clothing of the deceased, strands of hair, cloth fragments, bullets, slugs, broken-off knife blades, or other penetrating weapons, blood stains and stains of body discharges such as semen should be carefully preserved. Small loose objects which might be lost during the transfer of the body from the scene to the morgue, should be carefully preserved in labelled containers for subsequent study.

In one interesting case, the deceased was found lying dead on the roof of a tenement house, with a bullet wound through the head. A button and a torn piece of fabric to which it was attached, were found in the clenched

hand of the victim. These articles were quietly removed by the police officer, who subsequently made it his business to attend the wake which was held over the body of the deceased. One of the visitors to the wake, who came ostensibly to mourn, was observed by the police officer to be wearing an overcoat of the very same fabric as that found in the hand of the deceased and with a button missing, which had evidently been torn out. He was arrested by the police officer and when confronted with the button and fabric found in the hand of the deceased, which fitted exactly the torn area in his overcoat, confessed the murder.

In another case the body of an elderly woman who had been murdered was found in the rear of her small delicatessen store. The victim's throat had been cut deeply in several places. There were defense cuts on one hand and other evidences of a struggle. Several strands of hair were found in the hands of the deceased and removed by the medical examiner at the scene for examination later. All but one of these hairs were long and gray and similar to those on the victim's head. A single short dark brown hair was also found which microscopically was similar in color and in cross section to the scalp hairs of the assailant who was taken into custody later and confessed the crime.

The medical examiner also supervises and directs the preservation of implements, utensils, weapons, wearing apparel, furnishings, suspicious stains, blood stains, body discharges, food, drink, medicines and chemicals, which he thinks may have some bearing on the case. All such objects should be carefully labelled and wrapped for delivery by a police officer to the laboratories of the toxicologist, the serologist, or to the technical laboratory of the Police Department, for whatever examinations may be indicated. In handling and collecting such material, precautions must be taken not to mar fingerprints or to add fingerprints on weapons and smooth-surfaced objects. Firearms, bullets and cartridge shells, found at the scene, are gathered up by the police, examined for fingerprints and then removed for study and tests by ballistics experts.

After the medical examiner has completed his preliminary examination and has reduced all his findings to writing in a report as required by law, the police officer in charge of the case searches the clothing of the deceased for personal belongings, and subsequently delivers them to the custody of the property clerk at Police Headquarters. The personal belongings frequently reveal the identity, the occupation, habits and associations of the deceased.

If the identity of the deceased is unknown and there is reason to believe that he has a criminal record, finger prints may be taken at the scene for purposes of identification, but not until the medical examiner has had an opportunity to examine the body. Finger printing of the deceased at the scene should not be done in cases that may require an examination of the finger nail scrapings. Examination of such scrapings is indicated in cases of assault in which the victim may have struggled with and scratched the

assailant. Fragments of skin, hairs, cloth fibers, blood and other substances which may prove important as clues and as evidence may be obtained in this way. It is better procedure, if the deceased is known, to postpone fingerprinting until after the external examination of the body has been completed by the medical examiner at the time of the necropsy. Finger prints of the deceased, however, should be taken in every homicide.

The medical examiner then orders the removal of the body to the mortuary for necropsy. Care must be exercised during the transportation of the body, that it is not mutilated and that nothing is done to interfere with the anatomical lesions which are present on the surface. Rough handling of the dead body may produce confusing postmortem injuries. The clothing of the deceased, which must be carefully described in connection with the necropsy, must not be destroyed or unnecessarily soiled with extraneous dirt or with the body discharges of the deceased. A police identification tag filled out at the scene by the patrolman assigned to the case is sent along with the body.

### NECROPSY

In a homicidal case, the necropsy should be performed as promptly as possible, preferably by the medical examiner who saw the body and investigated the case at the scene where it was found. Whenever possible, the necropsy should be witnessed by another medical examiner, and this fact should be noted in the protocol.

### POLICE AND PERSONAL IDENTIFICATION OF BODY TO MEDICAL EXAMINER. FINGER PRINTING OF DECEASED

In addition to the police identification, which has already been discussed, the identity of the deceased is established by his relatives or friends, who must also identify the body to the medical examiner who performs or who has witnessed the necropsy. The personal identification must be sworn to in an affidavit by the person who makes it. Mistakes in identification both deliberate and unintentional have been made and should be guarded against. The persons making the identification should be questioned carefully as to their relationship to the deceased, the duration of their acquaintanceship, and the last time and the circumstances under which they saw the deceased alive. In doubtful cases, the person making the identification should be required to state the physical characteristics of the deceased including any distinguishing marks, deformities and scars on the body. A deliberate false identification of a dead body is a misdemeanor and is punishable by law.

Whenever possible, more than one personal identification should be taken and preferably by persons who will be available to testify, should the case come to trial. Identification by persons living in distant cities may create difficulties for the prosecuting attorney, should he find it necessary to subpoena them as identifying witnesses at the trial.

Finger prints are taken routinely by the Bureau of Identification of the Police Department of all persons who die by homicide. Such prints frequently prove valuable in helping to establish the identity and also the criminal record, if any, of a deceased person. The finger prints are also useful for comparison with finger impressions found at the scene. In this connection it would be helpful to have on file the finger prints of the medical examiner who may unwittingly deposit finger prints during his investigation at the scene.

#### BODY SHOULD NOT BE EMBALMED BEFORE NECROPSY

Under no circumstances should the body be embalmed before the necropsy, as the embalming process vitiates many chemical tests which may subsequently be found necessary. The formaldehyde in the embalming fluid renders the detection of alcohol and cyanide in the organs difficult if not impossible. Besides interfering with the proper toxicological examination of the organs, embalming also produces confusing artefacts in the body. The trocar punctures throughout the thorax and abdomen may cause considerable mutilation of the various organs and make difficult the interpretation of blunt force injuries of the hollow and solid organs and also the tracing of the exact course of a penetrating wound.

It is only when a body has to be exhumed for a belated necropsy not originally performed because homicide was not suspected, that embalming has proved useful because of its preservative effect on the tissues. The necropsy on an exhumed embalmed body has all the limitations of one performed on a freshly embalmed body. In addition the postmortem decomposition may be considerable despite the embalming.

#### RECORDING OF FINDINGS DURING PROGRESS OF NECROPSY

A well equipped necropsy room should be available, with good light and necessary instruments for the performance of the necropsy, which should be done carefully and completely. During the progress of the necropsy, the positive and also the negative findings are dictated to a stenographer. The inclusion of significant negative findings in the record indicates that the necropsy was performed understandingly and thoroughly. The value of carefully recording the negative findings in the necropsy is appreciated readily by any medicolegal pathologist who has had occasion to testify in court under cross-examination. The defense counsel in a criminal action may ask the medical examiner many questions about the necropsy. If the negative findings are not mentioned in the autopsy report, the opposing counsel may succeed in his attempt to create the impression that the necropsy was carelessly done and that certain details were perhaps overlooked.

A necropsy can be performed properly only once, and one poorly performed is perhaps worse than none at all. The curious notion that it can be satisfactorily done over and over again exists in the minds of many, judging

from the frequent reports in the newspapers, of bodies inadequately examined the first time, being exhumed for a second and even a third necropsy.

### EXTERNAL EXAMINATION OF DEAD BODY

The dead body should be carefully undressed and the clothing carefully laid aside for examination after the necropsy. In removing the clothes, care must be taken not to obliterate any cuts or bullet perforations or to soil them unnecessarily with blood or body discharges. The body is then weighed on accurate scales provided for the purpose, and its height measured. A large pair of wooden calipers is useful for the latter purpose and also for measuring the location of wounds on the body, with reference to their distance from the heel.

The external surface of the body is examined very carefully and described in considerable detail. The sex, color, approximate age, nutritional state, the skeletal and muscular development, the color, length, amount and distribution of hair, the appearance of the corneae and conjunctivae, the color of the irides, the appearance of the nose, ears, mouth, lips, gums and teeth should all be noted.

The extent of rigor mortis, the distribution and color of the postmortem lividity, any evidences of putrefaction, mummification and adipocere formation, postmortem mutilation and dismemberment by human agencies, post-mortem injuries by insects, crustacea and larger animals, and by mechanical, physical or chemical agents are carefully described; also tattoo marks, scars of old wounds, needle puncture scars of drug addiction, amputations, surgical scars, and the condition of the genitalia.

Evidence of bleeding from any of the orifices such as the nose, ears, mouth, and genitals or anus is noted; also the presence and location of any small dark blue postmortem hemorrhages known as Tardieu spots, petechial hemorrhages, purpuric spots, cyanosis or pallor of the skin or mucous membranes, subcutaneous emphysema, edema and icterus.

The hands are carefully examined and described, noting the development and the presence or absence of any wounds or unusual stains. The condition of the finger nails should be noted, and scrapings taken from under the finger nails for subsequent microscopic examination in certain cases. The size, location and condition of any surgical operation wounds are also described.

### EXAMINATION AND DESCRIPTION OF WOUNDS

The exact location, size, character and probable age of all wounds, even the most minute, should be recorded, and the presence of any vital reaction in and about any of the wounds should be noted; thus, the changed or faded color of a contusion, and any evidence of infection or inflammation in a lacerated, incised, stab or bullet wound, would indicate that it was inflicted some time before death. Old or recent wounds may be found on the same

body, along with fresh wounds, and these must be carefully differentiated and evaluated. A microscopic examination of tissue from a recent wound will show a characteristic inflammatory reaction, not to be found in a wound inflicted just before or at the time of death.

A correct estimation of the age of a wound is often difficult and may require a careful gross and microscopic examination. It is especially important in cases of violent death in which the deceased is found dead, or dies shortly after being found, of injuries sustained previously which were not immediately fatal. In many cases of fatal blunt force injury to the head or to the abdominal viscera, death is delayed; there may be no suspicion of an injury until the necropsy is performed. If a satisfactory investigation is to be made by the police in such cases, the medical examiner must not mislead them with a careless, arbitrary and inaccurate estimate of the age of the injury. The correct estimate may exonerate some person who is being held wrongfully as a suspect and direct the police investigation along successful lines.

#### PHOTOGRAPHY, DRAWING AND DIAGRAMMING OF WOUNDS

Wounds, especially when they are multiple or patterned, or in any way unusual, should be photographed. These photographs should reveal all the finer details of the wounds which show up best if the surrounding skin is washed clean of blood and then carefully dried. Extraneous objects should not be included in the photographs. With close-up bullet wounds, care must be taken not to wipe away powder residues too vigorously. When there is much smoke deposit on the skin, this should be photographed first and then carefully washed off to permit accurate delineation of the bullet perforation, the powder burn and the embedded powder grains. The smokeless powders now loaded into most pistol cartridges produce very little smoke deposit on the skin.

If possible the medical examiner should learn to take his own photographs and develop and print his own pictures, so that he may offer them in evidence at a subsequent criminal proceeding. If such photographs are taken or finished by a professional photographer, it will be necessary, if they are to be offered in evidence, to produce the photographer to testify that he made them. Drawings also serve a useful purpose; these may be diagrammatic. The diagrammatic representation of wounds is made easy if a large printed outline drawing of the front, back and side views of the body is available. These can easily be filled in and labelled to correspond to the description of the wounds in the protocol.

#### MEASUREMENTS

The location of wounds should be indicated by accurate and easily interpreted measurements of their distance from common fixed landmarks on the surface of the body. It must be borne in mind that the nature and location



of wounds must be made understandable to non-medical persons; for example, to the presiding judge, the counsellors and jury at a trial. The direction and length of the track of every penetrating laceration, stab or bullet wound, and the structures and organs through which the track of such wound passes, must be recorded.

It is practical to express measurement of distance in inches, as well as in centimeters, and weight in pounds and ounces, as well as in grams. This will prove useful when testimony is subsequently given in court, when the pathological findings have to be translated to an assemblage of lay persons, who may be unfamiliar with the metric system of measurement.

#### WHAT THE NECROPSY MUST REVEAL TO INDICATE HOMICIDE

The unsuspected, the possible and the obvious homicide are definitely established by the necropsy, which is the most important part of the post-mortem examination. The necropsy, to establish death by homicide, must reveal a cause of death consistent with such an interpretation. A wound or combination of wounds<sup>o</sup> of sufficient severity to produce an immediate or delayed fatal effect on the body must be demonstrated together with the effects produced. The fatal effects, or complications resulting from the wound or wounds may be shock (when the wounds are very severe), hemorrhage, asphyxia, infection, thrombosis or embolism, occurring singly or in combination. But whatever the fatal complication may be, it must be directly related to and caused by the primary wound or injury which must also be demonstrable. The fatal complication or effect is designated as the immediate cause of death. The wound or injury causing the complication is the primary cause of death. The relationship of the fatal complication to the primary wound must not be equivocal but definite, to establish that the death was caused by violence.

In a case of poisoning, the presence of poison in the body and its deleterious effects on the organs must be determined. In this connection certain poisons may be eliminated from the body before the victim dies of their deleterious effects. At necropsy, only the effects and not the poison will be found. In such cases it is important to learn whether any poison was detected in the patient during life. If it was not demonstrated in the patient, the findings at autopsy would be difficult to use as proof of poisoning in the absence of poison in the tissues.

Any natural disease process revealed by the necropsy must be evaluated as to whether it has contributed to the cause of death or has been entirely unrelated to it. Occasionally the necropsy in a suspected case of homicide will disclose that death was not caused by violent means, but entirely or in great part by natural causes. Before attributing the death to disease in the latter type of case, a complete necropsy should be performed, including an examination of the skull and brain, the organs of the neck, and the spine and spinal cord, despite the absence of any outward indications of violence to these

regions. If the necropsy does not reveal any evidence of physical violence or of obvious disease, the organs should be saved for chemical examination to determine whether or not poisoning has occurred, and pieces of tissue from the organs should be taken for histological examination to determine whether or not a disease process existed, which was not evident on gross examination.

### HOMICIDAL ASPHYXIATION

In many cases of homicidal asphyxiation, external signs of injury may be absent from the neck and the cause of death is revealed only after the exposure, removal and careful dissection of the organs of the throat and neck, especially the larynx, which may show evidence of injury or obstruction. In ligature strangulation and in choking, injuries of the larynx such as occur with manual strangulation are usually absent, the ligature or gag found in position on the body of the deceased together with the signs of asphyxiation indicating the nature of the case.

In smothering, the necropsy may only reveal evidence of asphyxiation, the suspicion of homicide arising from the investigation of the dead body at the scene and the surrounding circumstances. In cases of manual strangulation, the grouped abrasions on the neck produced by the fingers or finger nails of the assailant are not always present, especially in cases of "mugging" in which the assailant, approaching from behind, uses his forearm to compress the victim's neck.

### FATAL WOUNDS WITHOUT EXTERNAL EVIDENCE OF TRAUMA

Fatal wounds of the skull and brain such as penetrating stab wounds<sup>10</sup> and non-penetrating blunt force injuries can occur with little or no external evidence of injury. In figure 1, the small size and inconspicuous appearance of a fatal ice pick stab wound of the scalp is illustrated. The wound was originally concealed by hair. The weapon perforated the skull and brain. Injuries of the cervical spine or spinal cord may remain undetected unless the spinal canal is explored and the cord removed and examined. The application of a blunt force, such as a kick, or a blow with a stick to the abdomen, may cause a rupture or laceration of a hollow or solid viscus, without any external evidence of wounding. In several fatal shooting cases, the bullet perforated the orbit between the open eyelids. With the eyelids closed, the wound was not evident. In two of these the bullet passed through the inner canthus of the eye medial to the eyeball. In a third case, the bullet perforated a spectacle lens and then passed through the eyeball. When this body was found lying prone on the ground, the eye wound was not recognized and it was first thought that the deceased had died of natural causes and had sustained the abrasions on his face by falling. The eyeglasses of the deceased were found near the body; one lens was missing, the right one was still in place and was perforated and blood-stained. The homi-

cidal nature of the case was then apparent. At necropsy, the bullet which had perforated the spectacle lens and then passed between the eyelids and through the eyeball, was found in the brain. Photographs of the deceased without and with the eyeglasses in place are seen in figure 2. The photograph in figure 3 is that of a deceased person shot through the inner canthus of the left eye. The wound is completely concealed by the closed eyelids.



FIG. 1. Small fatal homicidal ice pick stab wound of frontal portion of scalp (arrow). Wound concealed by hair which has been cut away. Weapon penetrated skull and deeply into brain.

#### DISPOSAL OF BODIES BY DISMEMBERMENT AND BURNING

The mutilation and dismemberment of a murdered body may destroy all possibility of identification and determination of the cause of death. In many cases, however, the cause of death can be determined despite extensive mutilation of the murdered body by dismemberment, burning or by chemical agents.

In one case the head and all four dismembered extremities of a murdered



FIG. 2. *Left*—Homicidal bullet wound through right eyeball concealed by closed eyelids. *Right*—Photograph with eyeglasses in place to show bullet perforation in right lens. When body was first found bullet wound was not recognized. Eyeglasses of deceased found near body. Bullet recovered in brain.

body were recovered. Two blunt weapon wounds were visible on the top and back of the head and there were blunt weapon defense wounds on the right hand. The four extremities were found tightly packed in a wooden box in the entrance way to a store; the head rolled out of the back of a garbage truck making collections of refuse in the same neighborhood. Subsequently the hips and thighs were found but not the upper part of the torso. The skull was fractured and the brain lacerated. The larynx was also fractured.

Bodies found burned in conflagrations should always be examined with the possibility that the deceased had been murdered and then incinerated to destroy evidence of the crime. It is wise to examine the blood chemically

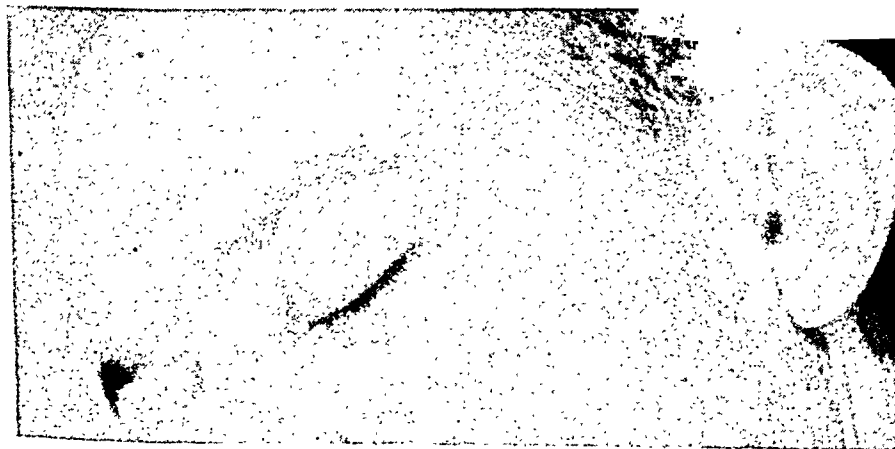


FIG. 3. Homicidal bullet wound through inner canthus of left eye concealed by closed eyelids. Bullet recovered in brain.

for the presence of carbon monoxide, the absence of which would indicate that the deceased was dead before the body was burned. There are several homicide cases recorded in the files of the Office of the Chief Medical Examiner of New York City in which charred bodies of persons at first thought to have been accidentally burned to death in conflagrations, were found at necropsy to have died of depressed fractures of the skull.

In a case investigated by Dr. Thomas A. Gonzales, Chief Medical Examiner of New York City, the charred dismembered head and torso and the charred segments of the lower limbs of the body of a negro were found among the embers of a bonfire in a vacant lot. Despite extensive incineration of the tissues, a comminuted depressed fracture was found in the occipital portion of the skull. That the deceased was dead when placed in the fire was corroborated by the absence of carbon monoxide from the blood. The perpetrator was apprehended and confessed that he had bludgeoned the victim to death, dismembered the body and tried to dispose of it by incineration in the bonfire.

#### SUBMERGED BODIES

In homicidal cases in which the body has been submerged for a variable length of time, in addition to the anatomical evidences of drowning and wounding, a chemical test for chlorides should be carried out on samples of blood removed from the right and left sides of the heart according to the method devised by Gettler.<sup>11</sup> The inhalation of salt water into the lungs is indicated by a higher concentration of chloride in the blood from the left side; the inhalation of fresh water produces a lower concentration of chloride on the left side. The test is vitiated by a patent foramen ovale and cannot be carried out in decomposed bodies in which the putrefactive gases have forced the blood out of the heart.

Penetrating stab wounds and bullet wounds and non-penetrating blunt force injuries are occasionally found in bodies recovered after varying periods of submersion. Suicidal injuries such as incised wounds of the throat and wrists are not infrequently encountered. Submerged bodies, especially those recovered from rivers and harbors in which there is a heavy shipping traffic, frequently show postmortem injuries which may be confusing even to the experienced observer.

An example of such postmortem injuries is illustrated by the case of a decomposed torso found floating in the Hudson River. Two days later, the right lower extremity with the distal half of the leg missing was found in the East River about five miles away. The next day, the corresponding left lower extremity was found floating in the Hudson River about two miles away. The torso and the extremities were obviously parts of the same body. By means of the cleaning and laundry marks in the clothing found on the left extremity, the body was identified as that of a 60-year old white man who one week before committed suicide by jumping off the back of a

ferry boat into the Hudson River. Prior to jumping he swallowed the contents of a bottle of poison which he purchased in a drug store earlier the same day. The body was probably dismembered by the propeller blades of the ferry boat. The identification definitely established the suicidal character of the death and the fact that the dismemberment occurred postmortem after submersion.

### PROCEDURE IN POISONING CASES

In cases in which there is a definite indication or suspicion of poisoning, the organs such as the brain, liver, kidneys, stomach and its contents, lungs and bones, and the blood and urine, should be saved for chemical examination. These should be carefully weighed and measured, placed in clean labelled containers without contamination, and promptly delivered and properly identified as to source, to the toxicologist. The careful examination of the organs for evidences of disease or traumatic injury should not be neglected, and pieces of tissue should be saved for microscopic examination. Many poisons produce characteristic histologic alterations, and certain disease processes, not visible grossly, which clinically simulate the action of poison, may become apparent.

Where the necropsy findings definitely point to a certain poison or group of poisons, the toxicologist should be so informed in order that he may directly test for the suspected substance. In the absence of such leading information, considerable time may elapse before the routine systematic analysis for all poisons will reveal the substance present. This delay may hamper the investigation of the case by the police authorities.

### DETAILS OF NECROPSY REQUIRING SPECIAL CONSIDERATION

The necropsy in a homicidal case involves much more than the mere determination of the cause of death. A considerable amount of information must be obtained in anticipation of questions which may subsequently arise in connection with it.

### SHOOTING CASES

The description of bullet wounds should include those details which help to indicate the distance from the body, of the weapon used in firing the shot. A contact bullet wound is produced when the gun is fired with its muzzle held against the skin and its appearance is fairly characteristic. The skin surrounding the perforation does not contain any embedded powder grains because the full effect of the discharge is blown into the track of the wound, which may be blackened and burned for a variable distance. The perforation in the skin varies in size and is often large and irregularly lacerated. However, it is sometimes small and regular in appearance. In some contact wounds, a distinctive abraded impression of the muzzle of the weapon is found on the skin.

The two photographs in figure 4 illustrate two different patterned impressions of the muzzle of a pistol on the skin in contact bullet wounds. In the picture on the left, the right temple reveals the clear cut impression of the muzzle of a 32-caliber Colt automatic pistol used by the deceased to commit suicide. In the picture on the right, there are three homicidal bullet wounds, one a closeup and two contact wounds. The contact wound on the cheek has an inverted keyhole pattern, the pyramidal shape of the abrasion (arrow) corresponding to the outline of the end of the rib found on top of the barrel of certain revolvers like the Iver-Johnson.

A close-up wound is produced when the weapon is fired at close range and characteristically reveals the effects on the skin of the powder grains and

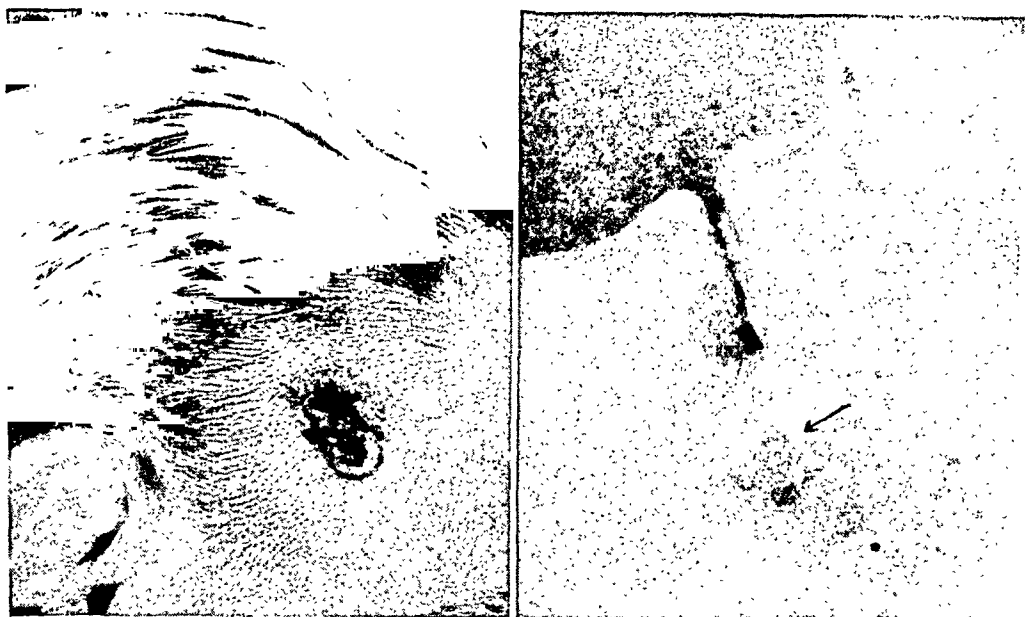


FIG. 4. *Left*—Patterned impression of muzzle of 32-caliber Colt automatic pistol on right temple. Suicidal contact bullet wound. *Right*—Patterned impression of end of rib on muzzle of revolver. Homicidal contact bullet wound.

flame of the discharge in addition to the bullet perforation. The distribution and appearance of the embedded powder grains, the extent of the burn and smoke deposit, and their relation to the bullet perforation should be carefully noted.

In a distant shot, the muzzle of the gun is held beyond the reach of the flame and powder grains of the discharge; the surface wound consists only of the bullet perforation and varies in appearance according to the angle at which the bullet strikes.

A valid opinion as to the distance from which a shot was fired, to cause a wound on a clothed part of the body can only be given after an examination of the clothing. The powder grains, flame and smoke of the discharge

in a close-up shot are deposited on the clothes and only the bullet may reach the skin, as in a distant shot.

### PRESERVATION OF BULLETS AND OTHER OBJECTS RECOVERED AT NECROPSY

All bullets and bullet fragments, shotgun pellets and slugs must be recovered from the body. In contact wounds inflicted with a shotgun, the felt wads of the cartridge may also be found. The bullets removed at the necropsy are an important part of the corpus delicti, and by their composition, caliber and rifling marks may be traced to one or more weapons used



FIG. 5. *Left*—Penetrating stab wound in right parietal portion of scalp. Note slight bulge produced by projecting end of underlying knife blade. *Upper Right*—Top of skull removed and laid back to show length of broken-off knife blade which penetrated skull and brain. Note stab wound in dura; large subdural hemorrhage flowed out and was collected in hollow of skull at time of autopsy. *Lower Right*—Broken-off blade embedded in block of bone removed at autopsy and offered as evidence at trial. Handle of knife with broken blade stump found on perpetrator, included in photo to show matching broken ends of blade. After being stabbed deceased chased his assailant for distance of a block.

in the commission of the crime. Occasionally, bullets of different caliber are recovered from the same body, indicating that more than one weapon was used in the shooting.

The bullets removed from the body must be carefully described and marked by the medical examiner for purposes of identification. Care must be taken during the removal and marking of a bullet not to mar any of the distinctive rifling marks on the sides of the missile because these marks are used for purposes of comparison with test bullets fired from the pistol believed to have been used in the crime. The bullets should be safely stored



in a locked container until they are delivered for testing to a member of the Ballistics Bureau of the Police Department, who will furnish a receipt for them; upon their return from the ballistics department, the medical examiner will give a receipt acknowledging the fact. These precautions are necessary in order that the bullets may be introduced properly by the medical examiner as evidence at any subsequent criminal proceeding.

Similarly, in stabbing cases, the broken-off fragment of any weapon, such as a knife blade, ice pick or scissors blade, found in the body should be carefully preserved as evidence and for future comparison with a weapon from which it may have been derived.



FIG. 6. *Left*—Small penetrating stab wound in forehead. *Right*—Calvarium and brain removed showing broken off closed scissors blades stuck in right frontal bone projecting into cranial cavity. The blades pierced the frontal lobe of the brain resulting in a delayed fatal hemorrhage.

If a broken-off knife blade is found embedded in bone which it has perforated, a block of the bone containing the blade can be removed with a saw or chisel and preserved as an exhibit which can be offered later in evidence to show the weapon and the extent of its penetration. An example of such a case is illustrated by the photographs in figure 5. The picture on the left shows a stab wound in the scalp beneath which a broken-off knife blade was found perforating the skull and underlying brain. In the top picture on the right, the skull cap has been removed and turned back to show the length and point of the blade which pierced the meninges and the brain. A large subdural hemorrhage was allowed to escape into the hollow of the skull before the photograph was taken. The perforation in the dura is readily seen. In the bottom picture, the broken blade in its undisturbed position in the bone is shown removed from the skull and placed next to the pocket knife

used by the perpetrator. The broken-off blade in the bone was admitted as evidence in the trial. In this case, the deceased, a 17-year old boy, after being stabbed in the head, ran a block after his assailant and attempted to strike him before collapsing. Death occurred rapidly because of the large subdural hemorrhage from the cut vessels on the surface of the brain. There was no bleeding along the track of the wound in the brain tissue.

In other cases of stab wounds of the brain the injured brain tissue may bleed slightly at first and the victim remain conscious for a variable period of time during which the nature and seriousness of his injury are not recognized. The entrance wound may be small. The sudden onset of secondary bleeding in the injured brain tissue causes rapid unconsciousness and death. In a case of this type, illustrated in figure 6, the victim was stabbed through the forehead with a closed scissors; the small entrance wound can be seen in the photograph on the left. He remained conscious and walked into the accident room of a hospital where he suddenly became unconscious and died two days later. In the photograph on the right, the broken-off scissors blades can be seen perforating the right frontal bone. There was a large hemorrhage into the frontal lobe of the brain which was pierced by the weapon.

Occasionally, a broken-off piece of a blunt instrument is found in a penetrating wound. Metallic fragments such as radiator ornaments, door handles and button fasteners, and glass fragments may be found in the body of a person fatally injured by an automobile. Such objects are important for purposes of comparison with the suspected damaged vehicle in "hit-and-run" automobile cases and should always be saved.

#### EXAMINATION OF SPINE

If there is any indication that the spine or spinal cord may have been injured in the track of a bullet or stab wound, such injuries must be definitely established by the necropsy. Aside from the relation of a spinal cord injury to the cause of death, the finding of such an injury may have considerable significance should the question subsequently arise as to whether or not the deceased could have walked after having received his wounds.

#### SEXUAL ASSAULTS

In homicidal cases, in which there is suspicion or evidence that a sexual assault, such as rape or sodomy, was committed on the deceased, the necropsy must include a careful examination of the genitalia and anal region to determine the presence of injury. Fresh and stained smears of secretions taken from the vagina and anal region and of any seminal deposits and stains on the pubic hairs and skin surrounding the vulva and suspicious stains on the undergarments should be examined for spermatozoa.<sup>12</sup> Ultraviolet light is helpful in rendering seminal stains on certain types of cloth more visible.

If many suspicious stains are found, the Florence test may first be carried out and only those stains reacting positively need be examined further for spermatozoa.

An attempt should be made to determine the group specificity of the seminal stains. The latter procedure should be carried out by a competent serologist. The organs of the deceased, especially the brain, should be examined chemically for the presence of poisons which might have been administered to the deceased to overcome resistance during the commission of the crime, and which might have caused the death.

### EXAMINATION OF STOMACH CONTENTS

In homicidal cases, the contents and the degree of digestion of any food in the stomach and intestines should be carefully noted. The presence of certain recognizable particles of food and the degree of digestion may suggest whether or not the deceased had recently eaten and in connection with other information may help in the determination of the postmortem interval and also in the identification of the deceased. The length of time that food remains in the stomach before passing into the intestine varies considerably and any opinion based on the necropsy stating the time before death that food was eaten should be guarded. In injured and comatose persons ingested food may remain in the stomach for days.

### TOXICOLOGICAL EXAMINATIONS

A quantitative chemical examination of the brain to determine the presence of ethyl and methyl alcohol should be carried out routinely in all cases of homicide in which the deceased has been found dead or has survived for less than 24 hours in the hospital after having received his injuries. If the survival period is longer than 24 hours, any ethyl alcohol present in the tissues will have disappeared by oxidation although methyl alcohol may persist for a longer time. The presence of alcohol in the brain indicates that the deceased had consumed it during the 24-hour period prior to death.

The amounts of alcohol recovered quantitatively in the brain are expressed by Gettler and Tiber,<sup>13</sup> in terms of plus amounts and are designated as: a trace, 1 +, 2 +, 3 + and 4 +. These designations correspond to amounts of alcohol as follows:

trace .....	0.005 to 0.02 per cent.
1 + .....	0.03 to 0.10 per cent.
2 + .....	0.11 to 0.25 per cent.
3 + .....	0.26 to 0.40 per cent.
4 + .....	0.41 to 0.60 per cent.

Amounts of alcohol above 0.25 per cent are considered indicative of "intoxication." The amount of alcohol recovered from the brain does not necessarily indicate the amount consumed. Persons addicted to alcohol are able to oxidize it more rapidly than those who are not and, therefore, may

consume more and have less residual alcohol in the brain after a certain period of time. In estimating the probable state of intoxication from the amount of alcohol recovered from the brain, the period of time that the deceased has survived since the last ingestion of alcohol must be considered. The amount of alcohol recovered at necropsy is not significantly altered by the postmortem interval.

Chemical examination for other poisons should be made in certain types of cases. Depressant poisons such as chloral, barbiturate compounds, morphine and hyoscine, chloroform and other anesthetic compounds, should be tested for in homicidal cases associated with robbery, sexual assault and criminal abortion where the deceased is found dead in the home or in a doctor's or midwife's office. In such cases, a routine systematic analysis for all poisons should be carried out on the organs.

#### EXAMINATION OF FINGER NAIL SCRAPINGS AND HAIR

The scrapings from under the finger nails and from the hands of the deceased should be carefully examined for minute fragments of skin, strands of hair and cloth fibers which the deceased may have removed from the assailant during a struggle. This procedure should be carried out in cases of homicidal strangulation, smothering and choking and in deaths from homicidal assault with blunt or sharp weapons.

It is useful to remove small tufts of hair from the scalp and other parts of the body of the deceased and to save them for future comparison with hairs found on subsequently confiscated weapons. Hairs from the deceased should be saved in homicidal cases where death has been caused by injuries of the head inflicted with blunt weapons and also in cases of death by "hit-and-run" automobiles in which some of the deceased's hairs may have been torn out and remained attached to various parts of the vehicle such as the bumper, fender or headlight. Vance<sup>14</sup> has described the technic and pointed out the medicolegal applications of hair examinations.

#### ROUTINE BLOOD GROUPING OF DECEASED

The blood group of the deceased should be determined in all cases of homicide. This information may prove very significant, in the event that a blood stain found on the clothing of a suspect is of the same group as the blood of the deceased and different from the suspect's own blood group; in such a case, there would be strong presumption as to the origin of the stain.

Blood stains on the clothing, suspected of belonging to the assailant and not to the deceased, should be grouped if possible, and the group compared with that of the deceased's blood and also with that of the suspect.

Wiener<sup>15</sup> has shown that by utilizing the four major blood groups O, A, B and AB of Landsteiner, the subgroups of A and AB discovered by von Dungern and Hirszfeld in 1910, the three blood types M, N and MN, and

type P, determined by the factors M and N, and P which were discovered by Landsteiner and Levine in 1928 and which are independent of the major groups, and the eight Rh blood types which have been evolved from the recent discovery of the Rh factor by Landsteiner and Wiener in 1937, it is now possible to distinguish 288 different kinds of human blood instead of the original four groups. The major blood groups and subgroups in all furnish six groups, O, A<sub>1</sub>, A<sub>2</sub>, B, A<sub>1</sub>B, A<sub>2</sub>B; there are the three independent blood types M, N, MN and two types determined by the presence or absence of factor P; the eight Rh blood types which are independent of the major groups and subgroups and of the types M, N, MN and of P, have been designated by Wiener as Rh<sub>0</sub>, Rh<sub>1</sub>, Rh<sub>2</sub>, Rh<sub>1</sub>Rh<sub>2</sub>, Rh-, Rh', Rh'', Rh'Rh''. By multiplying together the number of subdivisions in each of the above four categories, namely  $6 \times 3 \times 2 \times 8$ , the product of 288 different combinations or kinds of human blood is obtained.

The following homicide case <sup>16</sup> recently investigated by the Office of Chief Medical Examiner, the Police Department and the District Attorney's Office of New York County (Borough of Manhattan) is an excellent example of the value of group determinations in scientific crime detection.

At 2 o'clock in the morning, in the dim-out, a watchman of a building saw the figure of a man dragging a large object down the steps of an adjacent tenement house stoop and deposit it on the sidewalk a short distance away. The man then walked away. The watchman investigated the object and found it to be the body of a dead woman. While waiting for a police officer to arrive he observed the man who had carried the body return to the house and a few minutes later he saw him coming out again. The suspect was arrested but when confronted with the body stated that he had never seen it before. At the time of his arrest, he was carrying an almost empty wine bottle wrapped in newspaper under his arm; he admitted purchasing the bottle of wine in a neighborhood liquor store.

The examination of the body and subsequent necropsy by Dr. Morgan Vance, Deputy Chief Medical Examiner, revealed that death had resulted from strangulation. There were abrasions and a ligature mark on the neck. The distribution of the postmortem lividities indicated that the body had been moved after death and the disappearance of rigor mortis indicated that it had been dead for some time. A large amount of alcohol was found in the brain.

When the body was found the left shoe and stocking and the hat of the deceased were missing. Near the head there was a rolled up brown paper bag which contained the missing stocking. Several blocks away a package was found in a refuse can; it contained two men's shirts, a woman's hat and a left shoe similar to the right shoe of the deceased, and two men's handkerchiefs knotted together with several wisps of hair entangled in the knots. In the suspect's room a shiny dry stain was found near the bed on the oilcloth floor covering and a blood stain on the bed sheet. At the request of the

District Attorney investigating the case, the suspect consented to have his blood typed. The oilcloth covered with the shiny stain, the blood-stained bed sheet and the shirts and handkerchiefs found with the deceased's hat and shoe were sent to the serological laboratory of the Medical Examiner's Office for examination.

The following results were obtained by Dr. Alexander S. Wiener, Serologist of the Medical Examiner's Office. The deceased's blood was group A and tests on her tissues proved her to be a secretor of group A substance. The suspect was group B. The blood stain on the bed sheet by chemical and precipitin tests was proved to be human blood but there was not enough material for a group determination. The dry stain on the floor was found to contain albumin, nasal epithelial cells and also group A substance, the group being similar to that of the deceased. The shirts and handkerchiefs found in the package with the deceased's hat and shoe, contained group B substance which had been secreted in the sweat and nasal discharge of the person who had used them. The group substance in the shirts and handkerchiefs was therefore the same as that of the suspect. The hairs found in the knotted handkerchiefs were similar to those on the deceased's head. The brown paper bag containing the stocking, found near the head of the deceased, was traced to the liquor store where the suspect admitted he had bought the bottle of wine he was carrying when arrested. The wine had been wrapped in such a bag when it was sold.

The suspect at first denied any connection with the crime and was held as a material witness. When the significance of the incriminating scientific circumstantial evidence was explained to him, he confessed the murder, stating that he had manually strangled the deceased on the bed in his room, about twenty-four hours before removing her body to the sidewalk. He claimed that he strangled the victim because she had become drunk and noisy and had refused to leave his room after drinking most of his wine. After the murder he had placed the body face down on the floor during which time the secretion from the nose and mouth drained out on the oil cloth to produce the stain which contained the group A substance. He had used his soiled handkerchiefs as a ligature to keep the deceased's mouth closed. After having carried the deceased's body from his room, he had gone back and wrapped the soiled handkerchiefs and his shirts and the deceased's hat and left shoe in the package which he discarded in a refuse can several blocks away. When he returned again to the room, he found that he had overlooked a stocking and put it in the brown paper bag. He had this bag containing the stocking in his pocket when he was arrested but managed to drop it unnoticed near the head of the victim when he was asked to view the body.

#### EXAMINATION OF CLOTHING AS PART OF CORPUS DELICTI

The clothing of the deceased in a homicide case is an important part of the corpus delicti and must be carefully described and marked for identifica-

tion by the medical examiner. Blood stains, and cuts and perforations produced by weapons and missiles are noted, as well as their location in relation to the wounds on the body. The examination of the clothing, as already pointed out, is most important in shooting cases, enabling the examiner to determine whether a certain wound on a covered portion of the body resulted from a close-up or distant shot. The clothes are also helpful in determining the direction of a bullet track, in cases where the bullet has passed completely through the body, producing entrance and exit wounds which are not readily differentiated. In such cases, the bullet may pass out of the skin through the exit wound but not completely through the clothing, which circumstance will indicate the direction of the bullet.

In a recent murder trial in New Jersey<sup>17</sup> presided over by Judge Egbert Rosecrans, the defendant admitted the fatal shooting but claimed that he did it in self-defense and there seemed to be strong corroborative evidence that this was so. The fatal bullet had passed completely through the body. The victim was operated upon and during this procedure a bullet wound on the front of the abdomen was obliterated. A bullet perforation on the back was interpreted as an entrance wound by the physician who performed the necropsy. Because of this interpretation, the self-defense plea of the perpetrator was not believed and he was indicted and tried for the murder.

Upon inquiry it was learned that the clothing worn by the deceased when he was shot, had not been examined. Fortunately it had been saved and was examined during the trial. The fatal bullet had perforated all the garments in front but not in the back, indicating clearly that the bullet entered through the front of the body, a fact consistent with the claim of self-defense. The defendant was acquitted.

#### OTHER EXAMINATIONS CONNECTED WITH NECROPSY

A careful examination should also be made of any ligatures, gags or wads that may be found around the neck or mouth, or in the mouth and throat of the deceased, in cases of homicidal strangulation by ligature, and choking. Ropes, wires or any improvised ligature found on the extremities or body of a deceased person are described and saved.

#### PRESERVATION OF EVIDENTIAL MATERIAL

The clothing of the deceased and other evidential material, such as ligatures and gags, are carefully preserved and delivered by the identifying police officer to the prosecuting attorney for use in any subsequent criminal prosecution of the case. The clothing of the deceased person must not be returned to the family. In those cases where the deceased dies in the hospital some time after he has received his injuries, the hospital authorities must be instructed not to deliver the clothing of the deceased to members of the family, but to save it for subsequent examination by the medical examiner at the time of the necropsy.

POSTMORTEM FINDINGS AND CONCLUSIONS REPORTED TO POLICE  
AND PROSECUTING ATTORNEY

Upon the completion of the investigation and necropsy by the medical examiner in a case of homicidal death, the police authorities should be notified promptly of the findings in order to help them in their investigation of the crime. It is important to report cases of unsuspected violent death discovered at necropsy which are definitely or possibly homicidal. If the necropsy in an apparently suspicious case already under investigation by the police, does not reveal any evidence of criminal violence the police should also be informed of the findings.

The medical examiner's report is carefully corrected and a copy delivered to the prosecuting attorney. It is not permissible to divulge the findings in a homicidal case to any one else. Permission to inspect the postmortem records may be granted only by the district attorney.

In those cases which subsequently come to trial, the medical examiner is an important witness for the prosecution. However, he must always remember that he is not a prosecuting witness and must not be biased. His opinions should always be warranted by the findings in his investigation and necropsy. He should consider himself *amicus curiae*.

## SUMMARY

Inadequacies in the statutes pertaining to the Office of Coroner and Medical Examiner and in the organization and function of these medicolegal agencies are responsible for unsatisfactory postmortem investigation of homicide in most jurisdictions in the United States.

A fundamental defect in the statutes is the failure to recognize and provide for the fact that in many violent deaths there are not any externally obvious or suspicious signs of violence on the body of the deceased.

It is only by the routine investigation from the very beginning, of all sudden and unusual as well as suspicious and violent deaths, that unsuspected homicides will be detected. Paradoxically, those medicolegal systems which are concerned only with criminal deaths or obviously suspicious and violent ones fail most often to detect unlabelled homicides.

The medical examiner's system in New York City, Essex County (New Jersey), Nassau County (New York), and the State of Maryland, which was established in these places by almost identical statutes, possesses certain desirable features. It provides for the investigation of all violent, sudden, suspicious and unusual deaths and deaths which have occurred without benefit of medical attention. It functions independently of other government agencies insofar as the medical investigations are concerned and it places upon the medical examiner alone the responsibility and the authority for the necessity and the performance of the necropsy in any medical examiner's case. Every stage of the medical examiner's investigation is carried out by trained specialists in legal medicine.



The postmortem examination in a case of homicide properly commences with the investigation by the medical examiner, or other authorized and qualified medical person, of the dead body at the scene where it is found. A complete and careful necropsy is subsequently performed on the body of the deceased by the medical examiner to determine the cause of death. The necropsy should include certain routine and special examinations, not necessarily connected with the cause of death, but which may subsequently prove important in the development of the case.

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4. New York City Charter 1901, sections 1570 and 1571, as added by L. 1915, ch. 284, section 2, relate to the Office of Chief Medical Examiner:

"Section 1570: Organization of Office, Officers and Employees.—There shall be established the Office of the Chief Medical Examiner of the City of New York. The head of the Office shall be called 'Chief Medical Examiner.' He shall be appointed by the Mayor from the Classified Service and be a doctor of medicine, and a skilled pathologist and microscopist.

"The Mayor may remove such officer upon stating in writing his reasons therefor, to be filed in the office of the Municipal Civil Service Commission and served upon such officer, and allowing him an opportunity of making a public explanation. The Chief Medical Examiner may appoint and remove such deputies, assistant medical examiners, scientific experts, officers and employees as may be provided for pursuant to law. Such deputy medical examiners and assistant medical examiners, as may be appointed, shall possess qualifications similar to those required in the appointment of the Chief Medical Examiner. The office shall be kept open every day in the year, including Sundays and holidays, with a clerk in constant attendance at all times during the day and night."

"Section 1571: Violent and Suspicious Deaths; Procedure.—When, in the City of New York, any person shall die from criminal violence, or by a casualty, or by suicide, or suddenly when in apparent health, or when unattended by a physician, or in prison, or in any suspicious or unusual manner, the officer in charge of the station house in the police precinct in which such person died shall immediately notify the Office of the Chief Medical Examiner of the known facts concerning the time, place, manner and circumstances of such death. Immediately upon receipt of such notification the chief medical examiner, or a deputy or assistant medical examiner, shall go to the dead body and take charge of the same. Such examiner shall fully investigate the essential facts concerning the circumstances of the death, taking the names and addresses of as many witnesses thereto as it may be practicable to obtain and, before leaving the premises, shall reduce all such facts to writing and file the same in his office. The police officer so detailed shall, in the absence of the next of kin of deceased person, take possession of all property of value found on such person, make an exact inventory thereof in his report, and deliver such property to the police department, which shall surrender the same to the person entitled to its custody or possession. Such examiner shall take possession of any portable objects which, in his opinion, may be useful in establishing the cause of death, and deliver them to the police department."

"Section 1571 a: Autopsies; Findings.—If the cause of such death shall be established beyond a reasonable doubt, the medical examiner in charge shall so report to his office. If, however, in the opinion of such medical examiner an autopsy is necessary, the same shall be performed by a medical examiner. A detailed description of the findings written during the progress of such autopsy and the conclusions drawn therefrom shall thereupon be filed in his office."

"Section 1571 b: Report of Deaths, Removal of Bodies.—It shall be the duty of any citizen who may become aware of the death of any such person to report such death forthwith to the Office of the Chief Medical Examiner and to a police officer, who shall forthwith notify the officer in charge of the station house in the police precinct in which such person died. Any person who shall wilfully neglect or refuse to report such death or who, without written order from the medical examiner shall wilfully touch, remove, or disturb the body of any such person, or wilfully touch, remove, or disturb the clothing, or any article upon or near such body, shall be guilty of a misdemeanor."

"Section 1571 c: Records.—It shall be the duty of the Office of the Chief Medical Examiner to keep full and complete records. Such records shall be kept in the office, properly indexed, stating the name, if known, of every such person, the place where the body was found and the date of death. To the record of each case shall be attached the original report of the medical examiner and the detailed findings of the autopsy, if any. The office shall promptly deliver to the appropriate district attorney copies of all records relating to every death as to which there is, in the judgment of the medical examiner in charge, any indication of criminality. All other records shall be open to public inspection as provided in section fifteen hundred and forty-five. The appropriate district attorney and the police commissioner of the city may require from such office such further records, and such daily information, as they may deem necessary."

"Section 1571 d: Oaths and Affidavits.—The Chief Medical Examiner, and all deputy or assistant medical examiners, may administer oaths and take affidavits, proofs and examination as to any matter within the jurisdiction of the office."

See also revised New York City Charter 1938, ch. 39, sections 874 to 879.

L. New Jersey 1927, ch. 106 and L. New York 1936, ch. 879 pertain to the Office of Chief Medical Examiner in Essex County and Nassau County, respectively; also L. Maryland 1939, ch. 369.

5. Annual Statistical Reports of the Chief Medical Examiner of the City of New York.
6. Photographs of the undisturbed dead body at the scene in the first two of the following examples were reproduced in Helpert, M. *op. cit. supra*, no. 1, p. 167.
7. For the photograph of the undisturbed dead body at the scene in this case, see GONZALES, T. A., VANCE, M., and HELPERT, M.: Legal medicine and toxicology, 1940, D. Appleton-Century Co., New York, p. 277.
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16. Assistant District Attorney Louis A. Pagnucco of the New York County District Attorney's office supervised the investigation of this case and I am indebted to him for the interesting details.
17. State of New Jersey vs. Frank Pulsinelli, Warren County Court of Oyer and Terminer, December Term, 1940.

# CASE REPORTS

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## EXCESSIVE SELF-ADMINISTERED DOSAGES OF THYROID EXTRACT\*

By DAVID GOLDFINGER, M.D., *Chicago, Illinois*

THERE are numerous reports in the literature regarding the effects of thyroid feeding in animals. There are only a few reports dealing with the effect of large doses of thyroid in man. The following case report is of interest because of the huge doses of thyroid extract consumed over a period of one year, by an individual subsequently proved unstable, for the concealed purpose of self-destruction.

### CASE REPORT

On December 4, 1941, a white, married, 28 year old woman presented herself for weight reduction. The past history revealed the usual childhood diseases, a tonsillectomy at age 5, but no serious illness. At age 24 (1937) a Caesarean section was performed for placenta previa. The patient admitted previous medical care for weight reduction without results.

The physical examination revealed a well developed and overly nourished woman 5'3" (60.2 cm.), weighing 166½ lbs. (75.6 kg.). The head and neck were negative. The thyroid was not palpable. The lungs were clear. The heart was essentially negative. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic and the pulse rate was 72. The abdomen was protuberant with a healed hypumbilical surgical scar. The extremities and the reflexes were negative. The pelvic and rectal examinations were negative. The preliminary laboratory survey showed a negative urinalysis and negative blood count. The Kahn test was negative. The basal metabolic rate was plus 1 per cent. Fluoroscopy of the chest was negative.

The usual method of weight reduction by dietary restriction was explained to the patient, but she rejected this plan, asserting that simple dietary restriction had proved valueless in the past. She was given thyroid extract (U.S.P.XI) in daily doses of four grains with the usual dietary instructions. Weight reduction was slow, and on January 21, 1942, the dosage was increased to six grains, since there were no subjective complaints or cardiovascular effects. On May 7, 1942, the weight was 132½ lbs. (60.2 kg.), the blood pressure was 142 mm. Hg systolic and 72 mm. diastolic, and the pulse rate was 90. The administration of thyroid was stopped. The patient returned on June 2, 1942, weighing 136¾ lbs. (62.1 kg.), the blood pressure was 132 mm. Hg systolic and 74 mm. diastolic, and the pulse rate was 74. Thyroid (6 grains daily) was reinstituted. In two weeks she lost 7 lbs. (3.1 kg.), and the blood pressure and pulse rate again increased. The thyroid dosage was reduced and, because of nervousness, was stopped two days later. However, the nervousness and weight loss continued, and it was discovered that the patient's lack of response to sedation was because she had been surreptitiously taking 20 to 25 grains of thyroid daily throughout the summer. The patient had been despondent. In November, 1942, the weight was 103 lbs. (46.8 kg.), the blood

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From the Department of Medicine, Chicago Medical School.

pressure 120 mm. Hg systolic and 80 mm. diastolic, and the pulse rate 160. She was hospitalized, during which time it was discovered that she had taken approximately 100 grains daily for an unknown period. The basal metabolic rate was plus 34 per cent. The electrocardiogram showed (figure 1, A) a rate of 105, some slurring of the QRS complexes, and flattening of the T-waves. The patient received no thyroid after hospitalization but she refused to eat, and continued to lose weight,

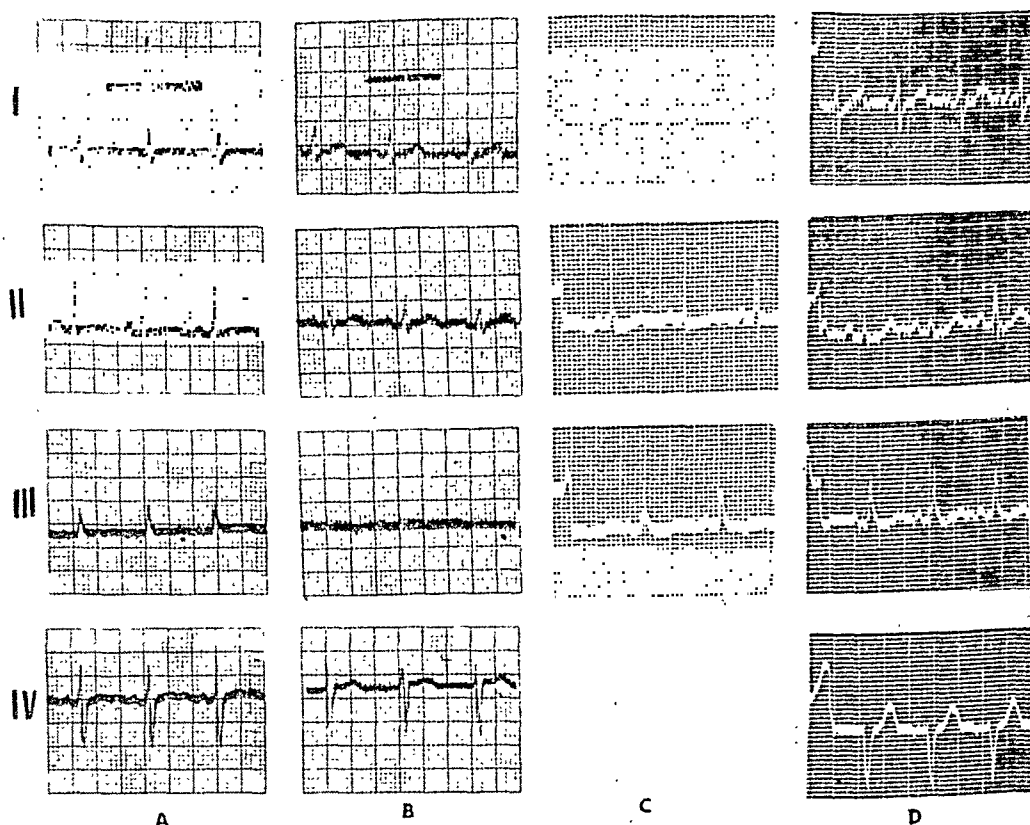


FIG. 1.

A. The electrocardiogram taken November 27, 1942 shows the standard leads and CF IV. The patient had consumed 100 grains of desiccated thyroid daily for an unknown period prior to this.

B. Electrocardiogram taken April 18, 1943, showing a lower standardization than A, slightly slower rate and T-waves of higher amplitude. No thyroid had been taken in four months.

C. Electrocardiogram taken March 30, 1944, showing the effects of digitalization; no thyroid had been ingested for six months.

D. Electrocardiogram taken January 20, 1945, nine days before sudden death. Thyroid and digitalis had not been administered.

finally reaching 80 lbs. (36.3 kg). She was sent to a mental hospital for psychiatric care.

The patient improved and gained weight. In April, 1943, she was allowed to go on walks alone. The electrocardiogram showed (figure 1, B) a rate of 97, and the T-waves in Leads I and II were definitely of much higher amplitude than in figure 1, A, and if the substandardization of this tracing be taken into account, comparatively, the T-waves in this tracing were much higher. Suddenly, the heart

rate and her nervousness increased, and it was discovered that she had purchased huge quantities of thyroid while unobserved, and had consumed doses conservatively estimated at 100 grains daily. Several thousand two-grain thyroid tablets were found hidden in the patient's room, as were also 15 empty bottles each of which had contained 100 two-grain tablets.

As far as is known, this thyroid feeding was discontinued in September 1943. After this the weight stabilized at 115 lbs. (52.2 kg). The tachycardia persisted, and on two occasions was slowed by digitalization, but the patient stopped this medication voluntarily because of nausea. An electrocardiogram, taken in February 1944, showed a rate of 123, and a tendency to right axis deviation; the ST segments were depressed (digitalis) and the T-waves, although blunted, were higher than in figure 1, A. Another tracing (figure 1, C), taken on March 30, 1944, showed a rate of 105, less tendency to right axis deviation than in the previous tracing, and the T-waves were blunted in Leads I and II, and inverted in Lead III. Lead CF IV was not included in the study at this time. The basal metabolic rate was plus 17 per cent on November 11, 1944. It was not possible to obtain actual metabolic rates in the interim, because of the patient's inability to cooperate. Quinidine sulfate was effective in reducing the heart rate on several occasions. She continued to be nervous, and, although her pulse remained below 85 while at rest, excitement and effort beyond ordinary activity readily produced tachycardia, which subsided irregularly with prolonged rest.

The electrocardiogram (figure 1, D) taken January 20, 1945, showed a marked uncontrollable somatic tremor. The rate is 120 and the T-waves are distinctly higher than when the excessive doses of thyroid had been taken. The patient had been worried and overly active, when suddenly while asleep on January 28, 1945, she was seized with severe precordial pain. Examination revealed a regular pulse rate of 160, and the blood pressure was 100 mm. Hg. systolic and 62 mm. diastolic. The patient was covered with a cold perspiration, and the other physical findings were negative. The patient failed to respond to the medication, and she died suddenly two and one half hours after the onset of pain. Permission for postmortem examination could not be secured.

#### COMMENT

An exactly similar case could not be found in the literature, since this patient consumed far more thyroid than has been previously reported (Daniel, 1928).<sup>1</sup> No attempt could be made to compute the total amount of thyroid ingested since no regular plan was followed after the first six months. The patient, in her good mental state, had testified concerning her former excessive dosages and her statements were corroborated by estimates made from empty bottles found in her environs.

It is possible that too much conservatism in thyroid dosage has been used by the medical profession in the past. The factor of safety is large, and although exceeded in this case, it is suggested that a much higher dose (U.S.P.) may be used where the thyroid effect is desired. Further work upon the amount of thyroid necessary to increase the basal metabolic rate would seem to be in order to establish effective, but non-toxic dosage levels.

The electrocardiogram taken during the first week of hospitalization showed flattened T-waves. Immediately preceding this, 100 grains of thyroid had been ingested daily for at least one week. In later curves, the T-waves are more upright, which becomes apparent when the error in standardization is taken into consideration. Hoffman,<sup>2</sup> in 1914, first commented on high T-waves in hyper-

thyroidism, believing that height paralleled pulse rate. Krumbhaar<sup>3</sup> confirmed these findings in 1918. White and Aub,<sup>4</sup> in the same year questioned this correlation. Pardee,<sup>5</sup> in 1928, confirmed the findings of high T-waves in hyperthyroidism, whereas Lewis,<sup>6</sup> in 1923, refuted them. Willius<sup>7</sup> noted high T-waves in thyrotoxicosis and Hamburger<sup>8</sup> noted high T-waves in several cases but without relation to the patient's condition or basal metabolic rate; Dow and Langley<sup>9</sup> in 1932, and McGuire and Foulger,<sup>10</sup> in the same year, gave similar opinions. The findings in this case report might indicate that the amplitude of the T-waves is decreased by thyroid feeding. Definite conclusions concerning T-wave involvement in thyroid feeding and thyrotoxicosis must await further study.

### SUMMARY

A case is reported in which huge doses of thyroid extract were ingested.

The weight loss amounted to more than half of the initial weight recorded; from 166½ lbs. (75.6 kg.), to 80 lbs. (36.3 kg.).

Electrocardiographic study at the height of thyroid feeding revealed T-waves of definitely decreased amplitude, and as the thyroid was withdrawn, the T-waves increased in amplitude.

The patient, prior to death, was in a normal mental state, and retained as her only obvious residue, an unstable vascular system, manifested by a sinus tachycardia which developed upon extraordinary activity.

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## PNEUMOCOCCIC MENINGITIS SUCCESSFULLY TREATED WITH PENICILLIN AND SULFADIAZINE \*

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THE prognosis in cases of pneumococcic meningitis has improved considerably since the advent of the sulfonamides and still more so since penicillin.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The mortality rate, however, continues to be quite high. Very few individual cases or series of cases treated with penicillin or penicillin and sulfa drugs have been reported. It is anticipated that as more cases are reported and thus more experience gained, further improvement in methods of treatment will follow and in turn a material reduction will result in both mortality and morbidity.

### CASE REPORT

A 22 year old white soldier sustained a .25 in. calibre gun shot wound of the face on July 11, 1944 when hit by a sniper's bullet. The entrance of the bullet was through the left temporal fossa and its exit was through the right nasal bone. It resulted in destruction of the left eye, compound, comminuted fractures of the left maxilla, orbital bones, nasal bones and nasal septum with extension of the fracture into the left frontal sinus, cribriform plate, left wing of the sphenoid and base of the left temporal bone, and a simple linear fracture of the left frontal bone. Following the injury, he was unconscious for four days. Two days after the injury a cerebrospinal fluid rhinorrhea was noted. Ten days after the injury meningitis, type undetermined, developed but promptly disappeared after penicillin and sulfadiazine were given. On August 2 enucleation of the remaining structures of the left eye was completed. A transfrontal bone flap was done on August 24 with the expectation of further operation 10 days later in an effort to stop the cerebrospinal fluid rhinorrhea. No further drainage occurred, however, after September 2. He gradually improved and, when his condition warranted it, he was evacuated to the States.

He arrived at this hospital December 29, ambulatory and in good condition except for a mild purulent conjunctivitis on the left. This was being treated symptomatically when, on January 8, 1945, he complained of headache, had a chill and a temperature elevation to 104°. He had been in the tropics in a known malarial area and this disease was suspected but several blood smears were negative. The following day he was comatose with a stiff neck and with positive Kernig and Brudzinski signs. A spinal tap revealed the fluid to be very cloudy and under markedly increased pressure. A smear of the fluid showed many gram positive diplococci resembling pneumococci and direct typing showed type 25. The cerebrospinal fluid culture, which showed profuse growth, subsequently confirmed this. On January 9, 30,000 units of penicillin were given intrathecally, 200,000 units intravenously and 6 grams of sodium sulfadiazine intravenously. On January 10, 50,000 units of penicillin were given intrathecally, 340,000 units intravenously and 6 grams of sodium sulfadiazine intravenously. Cerebrospinal fluid on this date was less cloudy but still under considerable pressure. Culture of the fluid showed only a slight growth of pneumococci. On January 11, 200,000 units of penicillin were given intravenously and 1 gram of sulfadiazine every four hours was started by nasal tube. On January 12 the cerebrospinal fluid was still cloudy. Forty-five thousand units of penicillin

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From Bushnell General Hospital.



were given intrathecally and 25,000 units intramuscularly were started every three hours. On this date the patient was still comatose and appeared considerably worse. A frontal temporal trephine was done by Major Max T. Schnitker, MC, AUS, Chief of Neurosurgical Section, in an effort to locate an extradural or frontal lobe abscess or focus. No abscess was found. During the operation, 50,000 units of penicillin were instilled into the left lateral ventricle. The patient's condition continued unchanged after the operation. He remained unconscious and totally unresponsive until January 14 when he suddenly roused from his coma, asked for a bed pan and shortly afterward wanted to discuss a furlough. On this date, after he had come out of his coma another 50,000 units of penicillin were instilled into the left ventricle. Following this he improved rapidly and had no apparent residual ill effects from his illness. Twenty-five thousand units of penicillin were given intramuscularly every three hours and 1 gram of sulfadiazine every four hours until February 4 at which time the cerebrospinal fluid cell count had returned to normal. Culture of the fluid was negative on and after January 12. Blood culture taken on January 9 was negative. Penicillin was instilled into the left orbital fossa throughout the illness. The patient received a total of 5,665,000 units of penicillin and 165.5 grams of sulfadiazine.

#### COMMENT

A mild conjunctivitis of the injured side existed at the time of admission to this hospital but there was no apparent break in the continuity of the tissues. The possibility of osteomyelitis of the damaged bony structures was considered, but could not be demonstrated. Meningitis occurred shortly after the injury and was supposedly cured by penicillin and sulfadiazine. However, the multiple fractures involving the nose, sinuses, and orbital structures, particularly in view of the cerebrospinal fluid rhinorrhea following the injury, may well have afforded a focus where the infection was dormant for many months.

The authors felt reluctant to do a trephine in the absence of any localizing neurological signs. However, since the patient's condition was very serious and there was a possibility of an abscess in the silent area of the frontal lobes, it was considered indicated. On the day of operation a spinal tap revealed that the cerebrospinal fluid contained a few flecks of fibrin which came through the needle with difficulty. It is quite possible that there was a blockage of the cerebrospinal fluid. At the time of the trephine penicillin was instilled into the ventricle and this may have been sufficient to have relieved any blockage which might have been present. However, culture of the ventricular fluid was sterile. Neurological complications<sup>9,10</sup> have been reported from intrathecal and intraventricular penicillin. This patient received the drug intravenously, intramuscularly, intrathecally and intraventricularly without any untoward effects, and although he was unconscious for five days, no residual neurological abnormalities were observed.

With large doses of penicillin given by other routes a sufficient amount may reach the cerebrospinal fluid<sup>11</sup> to warrant less frequent intrathecal injections, thus lessen the possibility of neurological complications.

Sulfadiazine was given concurrently with penicillin but it is believed that this patient's recovery would not have occurred without penicillin. The optimum dosage of penicillin has not been determined. However, it is more desirable to err on the side of overdosage than underdosage. The cerebrospinal fluid was sterile after the third day of treatment but in the absence of untoward reactions

and with the likelihood of relapse, medication was continued until the cerebrospinal fluid cell count returned to normal, which took a total of 27 days.

### SUMMARY

A case of pneumococcic meningitis, type 25, successfully treated with penicillin and sulfadiazine is reported.

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### SPONTANEOUS RUPTURE OF THE SPLEEN DURING MALARIA THERAPY; REPORT OF A CASE\*

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THE rarity of spontaneous rupture of the spleen in naturally acquired malarial infections has been expressed by Manson-Bahr,<sup>1</sup> Stitt,<sup>2</sup> and Osler.<sup>3</sup> Since the introduction of malaria as a therapeutic agent in the management of neurosyphilis, 31 cases of splenic rupture during treatment have been reported in the literature, either in detail or as personal references. Since this total cannot include unreported cases and cases that have not been recognized, the incidence of the complication probably approaches at least twice that number. Only one

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From Finney General Hospital.

known case of recovery has followed splenectomy.<sup>4</sup> In view of the gravity and unpredictability of this almost instantaneously fatal complication, it is felt that the addition of this case report will serve once again to remind clinicians of this unfortunate occurrence during a therapeutic procedure.

Cantacuzene,<sup>5</sup> Claude,<sup>6</sup> Weygandt,<sup>7</sup> Krumbhaar,<sup>8</sup> Herzig,<sup>9</sup> and Beckman<sup>10</sup> each vaguely referred to single cases of fatal splenic rupture encountered during the therapy of neurosyphilis. DeAsis<sup>11</sup> found two cases with ruptured spleens in a review of 101 cases of induced malaria, but full descriptions were never submitted. Bruetsch<sup>12</sup> reported the case of a 61 year old parietic who, following the fourth vivax paroxysm, suffered abdominal pain and circulatory collapse with death ensuing 24 hours after the onset of symptoms. At autopsy a 6 cm. tear was found along the lower margin of the spleen. Wile and Mundt<sup>13</sup> reported a single instance of splenic rupture in a series of 1026 cases. Their patient developed sudden cyanosis and dyspnea after the thirteenth paroxysm, and died within 45 minutes. Moore<sup>14</sup> reported two ruptured spleens in a series of 1600 patients treated with malaria therapy. Fong,<sup>15</sup> in a series of 1012 patients, encountered two cases, one occurring after the second paroxysm and the other after the eleventh paroxysm. Both spleens were enlarged, the first weighing 660 grams and the second 540 grams. Twitchell<sup>16</sup> reviewed the case of a 32 year old white male with general paresis who developed abdominal distention and vomiting after being placed on quinine therapy following the completion of 18 paroxysms. This patient reached operation, but died the following morning. An irregular 8 cm. tear was found in the hilus region extending inferoposteriorly. The spleen weighed 408 grams.

Polayes and Lederer<sup>17</sup> encountered a single fatality due to spontaneous rupture of the spleen in a 36 year old white parietic who had experienced five tertian paroxysms prior to the onset of stupor, dysarthria, inability to elevate the eyelids, tremor of the tongue and rather deep cyanosis. No local signs suggestive of abdominal hemorrhage existed and the cyanosis was thought to be the result of a pneumonic process also present. Autopsy revealed a spleen weighing 310 grams with several large capsular rents, the largest one measuring 6 cm. in length and extending deep into the pulp. These authors also abstracted the case reports of Alexander,<sup>18</sup> Hermann,<sup>19</sup> Tromner,<sup>20</sup> Bachmann,<sup>21</sup> Harris,<sup>22</sup> Clark,<sup>23</sup> and Robbins.<sup>24</sup> These seven fatalities occurred during induced vivax malaria, and the onset of collapse varied from the second to the tenth paroxysms. The remaining reports have been made by Jutz and Jacobi,<sup>25</sup> Adelheim (two cases),<sup>26</sup> Buttner and Hauer,<sup>27</sup> Jacobi and Herholz,<sup>28</sup> Palmgren,<sup>29</sup> Duprez,<sup>30</sup> and Currado.<sup>31</sup>

In Dattner's<sup>32</sup> review of over 5,000 cases treated in the Jauregg clinic, not a single case of spontaneous rupture of the spleen is reported. Although he feels that the arbitrary limit of eight malarial paroxysms used in their series may have accounted for the absence of this complication, at least nine of those reported in the literature developed before the eighth paroxysm.

#### CASE REPORT

*History.* A 38 year old white private was admitted to the Neurosyphilis Service January 30, 1945. In November 1942 a positive blood serologic reaction was discovered at a routine pre-induction examination, although the patient had no definite

history of a primary or secondary syphilitic lesion. He completed six weeks of arsenical and bismuth antisyphilitic chemotherapy in civilian life. On induction into the Army in April 1943, a syphilis register was opened with a diagnosis of neurosyphilis manifested by positive blood and spinal fluid serologic reactions. Over an irregular period of 10 months in the Army, the patient received a total of two neoarsphenamine, 36 mapharsen, and 16 bismuth injections. In May 1944, in Calcutta, India, a positive blood and spinal fluid serologic reaction was again discovered and

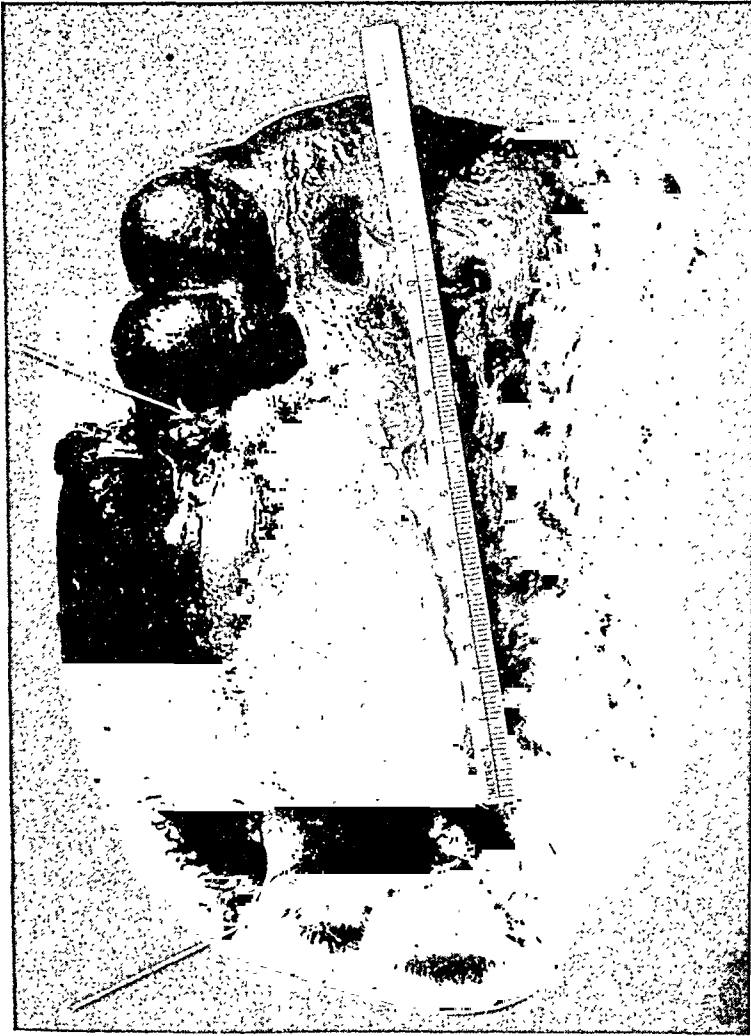


FIG. 1. Spleen, postero-medial aspect, showing spontaneous rupture. The extent of the 8 cm. laceration is marked by two arrows. Clotted blood can be noted between its margins.

he received eight injections of bismuth before returning to duty. He was rehospitalized in November 1944 for the completion of dental work. Blood and spinal fluid reactions were again found to be positive and he was finally evacuated to the Zone of the Interior for further evaluation and therapy. He had had gonorrhea at 16 years of age (1927). In the summer of 1944, while in India, he had an attack of malaria and received both quinine and atabrine for one week. He had no further malarial recurrences.

On admission, the patient complained only of difficulty in walking in the dark

and the occasional sensation of not knowing where his feet were. He had had headaches and dizziness while working in the sun, but had no history of cardiac, kidney or liver disease. General physical examination was essentially within normal limits. The spleen was not palpable.

*Neurological Examination.* Pupils reacted equally to light and accommodation; fundi were normal bilaterally. Deep tendon reflexes in the lower extremities were hypoactive and there was a loss of deep pain sensibility and diminution in vibratory sensation in both lower extremities. The remainder of the neurologic and psychiatric examinations was within normal limits.

*Course.* Blood serologic tests January 31, 1945 revealed a positive Kahn reaction. Spinal fluid examination January 31, 1945 revealed a positive Wassermann reaction in 0.1 c.c. dilution with 13 white blood cells per cubic mm., 68.2 mg. per cent total protein and a colloidal gold curve of 3443210000. Electrocardiogram and chest roentgenogram were normal and the remainder of the laboratory examinations were within normal limits.

Because of this patient's history of previous natural malaria in India, he was inoculated February 6, 1945 with the DuBose strain of Southwest Pacific vivax malaria. Following a pre-patent period of four days and an incubation period of five days, he developed a quotidian malarial cycle with an early remittent type of temperature. His course was uncomplicated until the onset of his twelfth paroxysm on February 23, 1945. At 12:00 noon February 23, 1945, the patient complained of a moderate aching pain over the precordium and the left anterior chest wall with no radiation to arms or abdomen. He had a severe malarial rigor at 12:10 p.m., and at 2:30 p.m., following the completion of his chill, he became mildly dyspneic, but extremely restless and delirious. His pulse rate was 144, blood pressure 70 mm. Hg systolic and 45 mm. diastolic, heart sounds fair, chest clear, except for a few râles at the right base posteriorly. The abdomen was soft. The liver and spleen were not palpable, and no edema was present. His temperature was 103.8° F., although all four extremities were cold and clammy. He received  $\frac{1}{6}$  grain of morphine and an oxygen mask was applied. During the next 15 minutes his status deteriorated rapidly. The blood pressure could not be recorded and the pulse rate was 150 to 160 with fair heart sounds. Respirations increased to 40 per minute and then became Cheyne-Stokes in nature. Artificial respiration aided by an oxygen tent was of no avail. He had received 0.2 gram of thio-bismol at 2:35 p.m. intramuscularly in an effort to interrupt his next paroxysm, and a plasma transfusion was being started when the patient died at 3:05 p.m. February 23, 1945. Respirations ceased shortly before the heart beat. An electrocardiogram taken one hour before death revealed no changes other than a marked sinus tachycardia.

*Summary of Necropsy Findings* (Necropsy performed by D.F.M.): The immediate cause of death was exsanguination and circulatory failure resulting from spontaneous rupture of the spleen. The underlying cause of death was therapeutic malaria administered in the treatment of *tabes dorsalis*.

*Spleen:* Weight 675 gm. after removal. The capsule showed two irregular linear vertical lacerations (figure 1). One tear was on the lateral convex surface measuring 8 cm. in length and the other on the medial concave surface measuring 4 cm. covered with a dark red, currant jelly, blood clot. Blood clot separated the capsule from the underlying splenic tissue at the edges of the lacerations. The capsule was thin, the edges rounded. The consistency was soft and markedly friable. The spleen was dark, reddish-blue in color. The cut surface was coarsely granular, dark-red and diffuent in appearance. The pulp was exceedingly friable. Microscopic examination showed the tear of the capsule with hemorrhage. The capsule was very thin. The malpighian bodies and trabeculae were widely separated, resulting from the marked proliferation of reticuloendothelial cells of the red pulp and

congestion of the sinusoids with red blood cells and mononuclear cells. The sinusoids were lined by large endothelial cells with enlarged, elongated nuclei. They contained many mononuclear histiocytic cells displaying ameboid shapes containing clear vacuoles and some dark brown granular malaria pigment. The malpighian bodies were compressed and the germinal centers were small. Large foci of interstitial hemorrhage with coarse hemosiderin deposits were noted throughout the splenic pulp. Neutrophils were rare. The endothelial lining of the small veins showed marked swelling and in some areas subintimal infiltration of mononuclear histiocytes, lymphocytes and plasma cells.

Numerous red blood cells showed *Plasmodium vivax* parasites in ring and schizont stages of development after staining in 4 per cent Giemsa stain overnight.

Liver: Weight 2100 gm. The surface was dark, reddish-tan and finely granular. The edges were rounded. On section the cut surface was dark, reddish-tan in color and was more friable than normal. The normal hepatic pattern was present on microscopic examination but there was moderate thickening of the periportal connective tissue with infiltration by many round cells and occasional histiocytes. The Kupffer cells were swollen and contained reddish-brown granular pigment. The hepatic cells showed cloudy swelling and finely granular yellowish-green pigment in their cytoplasm. Occasional foci of interstitial hemorrhage were present. The small bile ducts appeared normal. The portal veins contained several mononuclear cells.

Lungs: The right lung weighed 300 gm., the left lung 320 gm. Both lungs showed a moderate amount of coal pigment. The upper lobes contained a moderate amount of frothy pink fluid. Both lower lobes showed moderate atelectasis.

Heart: Weight 275 gm. Essentially normal except for pale color.

Pancreas: Weight 100 gm. Essentially normal.

Adrenals: Normal in size and shape and location. The right adrenal was covered with some clotted blood but on section appeared normal. Microscopic examination showed marked congestion of the vessels of the cortex.

Kidneys: The right kidney weighed 140 gm., the left kidney 150 gm. Gross examination essentially normal. The glomeruli appeared normal. The epithelium of the tubules displayed moderate cloudy swelling. The descending loops of Henle contained some amorphous pink-staining material. The interstitial tissue of the medulla contained numerous enlarged venules and capillaries.

Lymph Nodes: All lymph nodes showed slight generalized enlargement. On microscopic examination the reticulo-endothelial cells were increased in number and in size. The germinal centers appeared decreased in size. The sinuses were markedly dilated and contained numerous large histiocytic mononuclear cells which showed little phagocytic activity.

Brain: Weight 1340 gm. The cerebral vessels showed marked congestion. The cut surface displayed prominent congested vessels but no areas of softening or increased density. Microscopic examination displayed engorgement of the blood vessels with moderate perivascular lymphocytic and plasma cell infiltrations. The perivascular spaces were widened and contained a few histiocytic mononuclear cells. The parenchymal brain cells appeared essentially normal.

Spinal Cord: Microscopic examination revealed moderate perivascular, chronic inflammatory infiltration. There was a decrease in the cellular elements in the posterior horns with a relative increase in neuroglial tissue.

#### COMMENT

Although chronic enlargement of the spleen following recurrent attacks of natural malaria has been offered as an explanation for splenic rupture, it is

known that this complication develops much more commonly during therapeutic malaria than in the naturally acquired disease in which it rarely occurs. With the exception of the case herein reported, in which an attack of natural malaria preceded the therapeutic inoculation by approximately six months, most of the ruptures during therapy occurred in patients experiencing primary malarial attacks.

The differentiation between traumatic and spontaneous rupture of the spleen in malaria-treated cases is often difficult to evaluate because so many of the patients are restless and disturbed during treatment, incurring minor injuries probably sufficient to cause rupture in an enlarged spleen pathologically altered by the malarial process. Trauma could not be indicted as an etiological factor in this case report, unless the severe malarial rigor followed immediately by collapse be considered the equivalent of a traumatizing incident. Nevertheless, patients receiving malarial therapy should be handled with extreme caution in an effort to prevent even insignificant injury to the chest or abdomen.

Polayes and Lederer<sup>17</sup> are of the opinion that the increase in fibrous tissue in the splenic capsule and septa with resultant loss of elasticity, as reported by Bigland<sup>33</sup> and his associates in more than 97 per cent of 390 cases of syphilis of the central nervous system, predisposes to spontaneous rupture. The usual changes considered as predisposing factors, namely enlargement and softening, were not present in the spleens of patients suffering from neurosyphilis prior to the induction of malaria, according to these authors. The necropsy findings in several of the 31 cases of spontaneous rupture reviewed above revealed thickened splenic capsules partly adherent to the diaphragm in some cases, and merely firm and brittle in others. In Bruetsch's case,<sup>12</sup> one portion of the capsule was actually the seat of cartilaginous changes. Therefore, it seems rather likely that fibrosis and thickening of the splenic capsule, whether occasioned by a syphilitic process or by repeated attacks of malaria, act to restrain the splenic expansion which normally occurs during malarial infection as a result of the destruction of erythrocytes and proliferation of the reticulo-endothelial system. Since this expansion can only take place where normal elasticity remains, rupture in some cases may, therefore, depend upon the degree of engorgement, precipitated perhaps by the added insult of some injury.

### SUMMARY

1. A case of spontaneous rupture of the spleen during vivax malaria therapy in a patient with early tabes dorsalis is reported.
2. Reports of 31 similar cases of spontaneous splenic rupture, appearing in the literature, are mentioned.
3. Etiological factors are briefly considered.

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## IDIOPATHIC DILATATION OF THE COMMON BILE DUCT WITH COEXISTENT PRIMARY HEPATIC CAR- CINOMA: REPORT OF A CASE \*

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*Introduction.* Two rare diseases, idiopathic dilatation of the common bile duct (choledochus cyst) and hepatic carcinoma, found in the same youth, are a unique combination. No similar case studies have been described or referred to in the medical literature. The coexistence of these abnormalities of the biliary system suggests that the choledochus cyst was the precursor of the malignancy of the liver.

A complete report of such a case with autopsy observations is presented.

### CASE REPORT

First admission (July 16, 1943 to August 13, 1943). J. W. A., a 17 year old white single farm-hand, entered Vanderbilt University Hospital complaining of jaundice and swelling of the abdomen.

*Present Illness.* Though his older sister stated that the patient's skin had a yellowish tint when he was a small baby less than a year old, it was only in the eight years preceding admission that the patient himself noted any abnormalities. Each spring since the age of nine he had developed episodes of jaundice associated with light stools and dark urine. There was no associated pain, and these attacks lasted usually from two weeks to two months and disappeared spontaneously with no sequelae.

However, the episode starting in April, 1942 persisted throughout the entire year up to the time of entry in July, 1943. During this time he had light brown stools, dark urine, and occasionally pruritus. Two months before admission he began to feel weak, developed malaise, and gradually lost 10 pounds in weight.

Five weeks before admission to the hospital his abdomen began to swell. Two weeks later he developed abdominal pain for the first time. This was severe, localized in his right upper abdomen, lasted one day, and was relieved by codeine. His local physician told him that his liver was enlarged. For two days prior to admission the patient had constant lower abdominal pain and some difficulty getting his breath when lying flat in bed.

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There had been no vomiting, tarry or bloody stools, or constipation. Eructations and a burning sensation in his "stomach" had occurred whenever he ate fatty foods during the previous several years.

*Past History.* The patient had had the common diseases of childhood. His habits had been regular. He very rarely drank alcoholic beverages. He was never exposed to any known harmful chemicals, nor did he use any unusual drugs.

*Family History.* The father, mother, and seven siblings were living and well. There were no apparent familial diseases, and no condition similar to that of the patient was known to be present in the family.

*Physical Examination.* Temperature 101° F. Pulse 90. Respirations 28. Blood pressure was 105 mm. Hg systolic and 75 mm. diastolic.

*General Appearance.* The patient was a deeply jaundiced, underdeveloped, undernourished, red-headed, freckle-faced youth of about 17 years who appeared to be chronically ill. He seemed quite uncomfortable and was propped up in bed breathing rapidly, complaining of tightness in his enlarged abdomen.

The skin was yellow in color with several scattered small excoriated areas from scratching. The head and neck were normal. There was no lymphadenopathy. The sclerae were icteric but otherwise the eyes were negative.

The thorax was symmetrical, showing poor expansion. The thoracic wall was thin and showed flaring of the lower rib margins. Both leaves of the diaphragm were high posteriorly and moved very little on deep inspiration. The area of liver dullness extended up to the level of the fourth rib anteriorly on the right side. Vocal fremitus was normal. The breath sounds were puerile. There were no râles or friction rubs. The heart was negative in all respects.

The abdomen was very protuberant, the skin being tightly stretched and containing prominent veins over its upper portion. Fluid wave and shifting dullness were present. A tender grossly lobulated liver edge of firm consistency was felt four fingers'-breadth below the right costal margin. The spleen was felt two fingers'-breadth below the left costal margin on inspiration. There were no other palpable masses or organs. The remainder of the examination was negative.

*Laboratory Data.* The urine was red-brown in color, with a specific gravity of 1.020. Albumin and sugar were absent, though bile was present. Urobilinogen was present in a 1:16 dilution. There were occasional white blood cells in the uncentrifuged specimen.

The cell counts were red blood cells 4,500,000 and white blood cells 13,750 per cubic millimeter. Hemoglobin was 13.0 gm. per 100 c.c. The differential count was as follows: 79 per cent polymorphonuclears, 19 per cent lymphocytes, and 2 per cent monocytes. Sedimentation rate (Wintrobe, corrected) was 36 mm. per hour and a packed cell volume of 39 per cent. Mean corpuscular volume was 86.6 cubic micra, mean corpuscular hemoglobin 28.8 micrograms, and mean corpuscular hemoglobin concentration 33 per cent.

Other blood studies were as follows: icterus index 27; serum bilirubin 6.8 mg. per cent; coagulation time 4 minutes; bleeding time 3½ minutes; total serum protein 5.74 gm. per cent (3.19 gm. albumin and 2.55 gm. globulin); non-protein nitrogen 30 mg. per cent; cholesterol 313 mg. per cent; Kahn reaction negative.

The stool was light brown in color with the presence of bile. No occult blood, parasites or ova were found.

*Special Tests.* A red blood cell fragility test showed a normal range for hemolysis. Prothrombin time was 45 per cent of normal. The tourniquet test indicated no increase in capillary fragility. The bromsulphophthalein test for liver function showed a 52 per cent retention of the dye in 30 minutes. Hippuric acid test for liver function revealed a negligible amount excreted in the urine in one hour.

Ascitic fluid: This was sterile on culture. The specific gravity was 1.018. The

cell count was 6,959 with a preponderance of normal small lymphocytes and macrophages. Total protein was found to be 4.13 gm. per 100 c.c. of fluid; foam and Gmelin tests were positive for bile.

On chest fluoroscopy no pulmonary abnormalities or pleural effusions were noted. Both leaves of the diaphragm were elevated. The heart was normal.

A gastrointestinal series showed no intrinsic lesion of the duodenal cap; however, along the inferior medial aspect there was a pressure defect (possibly due to liver). The arch of the duodenum and its descending portion appeared to be widened as if a mass were interfering between the first and third portions of the duodenum. The mucosal pattern of the duodenum was normal. A flat film of the abdomen indicated general density in the upper abdomen probably due to enlarged liver and spleen.

Biliary drainage was unsuccessful.

*Course in the Hospital.* The day after entry abdominal paracentesis yielded 2400 c.c. of cloudy, green-yellow fluid which relieved the orthopnea and the low abdominal pain. This procedure was repeated five days later and 4600 c.c. of bile-stained fluid were obtained. In the following two weeks the patient received two liters of blood plasma and 15 c.c. of crude liver extract intramuscularly. He was also placed on a high carbohydrate, low fat, adequate protein diet with added vitamins. Twenty-five days after entry another abdominal paracentesis resulted in 4300 c.c. of bile-stained fluid. This procedure again relieved his recurrent abdominal discomfort.

Throughout his stay he had a daily fever varying from 99° to 101° F. There was little change in the size and shape of his enlarged liver and spleen. His icterus index had decreased to 9, his serum bilirubin to 2.44 mg. per cent, and his bromsulphonphthalein retention in 30 minutes was 40 per cent on the twenty-sixth hospital day. On discharge three days later his weight was 102 pounds, 17 pounds less than upon entry.

*Clinical Diagnosis.* Biliary cirrhosis of the liver due to repeated bouts of catarrhal jaundice.

Second admission (August 22, 1943 to death on August 27, 1943). Nine days after discharge, the patient reentered the hospital complaining of enlargement of the abdomen and a productive cough.

*Interval Note.* The patient developed increasing anorexia and nausea. He vomited a couple of days after being home. His abdomen again started to swell, and he developed an aching pain in his left upper abdomen, just to the left of his umbilicus. Three days before reentry he developed a productive cough, but no hemoptysis or pleuritic pain. He developed malaise and thought that he had a fever. He noted that an area over his enlarged liver had suddenly become more prominent and was tender to touch.

Physical Examination: Temperature 100.8° F. Pulse 140. Respirations 36. Blood pressure was 90 mm. Hg systolic and 60 mm. diastolic.

General Appearance: He was an acutely ill, cyanotic, dyspneic, emaciated youth with an anxious facial expression, coughing frequently. The skin was yellow in color with a loss of normal subcutaneous fat and very dehydrated.

Examination of the lungs showed vocal fremitus to be increased over both lung bases posteriorly. There was dullness over the same areas with bronchial breath sounds. Harsh bronchovesicular breath sounds were heard everywhere. Coarse moist râles were heard over both lungs posteriorly, and a friction rub was present over the left lower chest anteriorly and laterally.

The abdomen was distended with fluid and, as before, an enlarged liver was palpated four fingers'-breadth below the right costal margin. A large nodule about 8 cm. in diameter was felt in its lower border in the mid-epigastrium. The spleen was felt at the left costal margin.

Except for cyanosis of the nail beds the remainder of the examination was negative.

*Laboratory Data.* The urinary findings were the same as before.

The blood counts were red blood cells 4,600,000 and white blood cells 23,700 per cubic millimeter. The hemoglobin was 14.2 gm. per 100 c.c. The differential count was as follows: 85 per cent polymorphonuclears (81 per cent segmented, 3 per cent non-segmented, and 1 per cent basophiles), 11 per cent lymphocytes, 2 per cent monocytes, and 2 per cent smudges.

Other blood studies were as follows: icterus index 12; serum bilirubin 2.9 mg. per cent; non-protein nitrogen 41 mg. per cent; total serum protein 5.73 gm. per cent (3.12 gm. per cent albumin and 2.61 gm. per cent globulin).

In the stool bile was present, but no occult blood, parasites or ova were found.

The sputum was mucoid and without acid-fast bacteria. Culture revealed pneumococci, *Staphylococcus aureus*, and non-hemolytic streptococci.

Roentgenologic examination of the chest showed extensive exudation and partial consolidation which almost completely obliterated both lung fields.

*Course in the Hospital.* After an abdominal paracentesis removed 3500 c.c. of bile stained fluid from the abdomen, the patient was started on sulfadiazine and was placed in an oxygen tent. He was given a 500 c.c. plasma transfusion the second day. His temperature varied between 99° F. and 101.2° F., and his pulse and respirations remained fast over the next four days. During this time the mass felt in the liver continued to enlarge rapidly and caused the patient much pain locally. He gradually grew worse and died on the fifth hospital day.

*Diagnoses.* Biliary cirrhosis of the liver, possible primary carcinoma of the liver, pneumonia.

Postmortem Examination (By Dr. James N. Owens, Jr.): The autopsy was begun one and one-half hours after death on the body of a fairly well developed but cachectic male which appeared older than the stated age. The skin color was yellow, the lower costal margins were symmetrically flared outward, and the abdomen was large and tense. After the usual incision was made, the following observations were made:

*Peritoneal cavity.* This was filled with about 2500 c.c. of icteric fluid. There were numerous fibrinous adhesions between the liver and the anterior parietal peritoneum. Numerous umbilicated nodules were present on the peritoneum of the anterior abdominal wall and along the course of the pancreatic lymphatics as well as the mesenteric attachments of the stomach. The omentum was studded with similar nodules. The liver was roughly nodular and extended 10 cm. below the right costal margin at the anterior axillary line and 6 cm. below the left costal margin at the left anterior axillary line. There was a large ovoid semifluctuant whitish-gray mass present beneath the head of the pancreas so that the latter was compressed about this mass. The remaining organs were normally disposed.

*Pleural cavities.* No free fluid was present. Numerous small yellow-white nodules were scattered over the right parietal pleura. The left pleural cavity showed fibrin deposited over all its surfaces.

*Pericardium and heart.* Normal.

*Lungs.* The right lung weighed 1130 gm., the left 1500 gm. Numerous small, whitish, reticulated lines were seen beneath the pleura as well as numerous raised, spherical, yellow-white to brown nodules several millimeters in diameter. The parenchyma of both lungs was diffusely infiltrated with white-yellow tumor tissue (figure 1).

*Gastrointestinal tract.* This was normal. The opening from the biliary tract into the Ampulla of Vater was patent as was demonstrated by pressure on the gall-bladder. The region between the gall-bladder, duodenal cap, and transverse colon was occupied by a large mat of fibrous tissue.



FIG. 1. Section through left lung which is diffusely infiltrated with tumor tissue.

*Liver and associated structures.* The liver was enlarged and together with the stomach, extrahepatic biliary tract, duodenum and pancreas weighed 4120 gm. Several white-yellow, irregular, umbilicated tumor nodules were seen on its surface, most being on the left lobe. A large tumor mass 10 cm. in diameter occupied most of the quadrate

lobe adjacent to the falciform ligament. This projected up 2 cm. above the surrounding liver tissue anteriorly. On sectioning the liver it was observed that the major intrahepatic bile ducts were dilated to over 3 cm. in diameter and their walls were thickened. A spherical, enlarged, cystic common bile duct measuring 13 cm. in diameter was fluctuant to palpation, was externally a yellow-brown color, and was encircled by the duodenum (figure 2). When incised, a large quantity of dark green viscid bile escaped. Its wall was white and fibrous, measuring 2 to 3 mm. in thickness. The two hepatic ducts were dilated to about 15 mm. in diameter and communicated freely with the dilated common duct. There were a small fold and a dimple on the

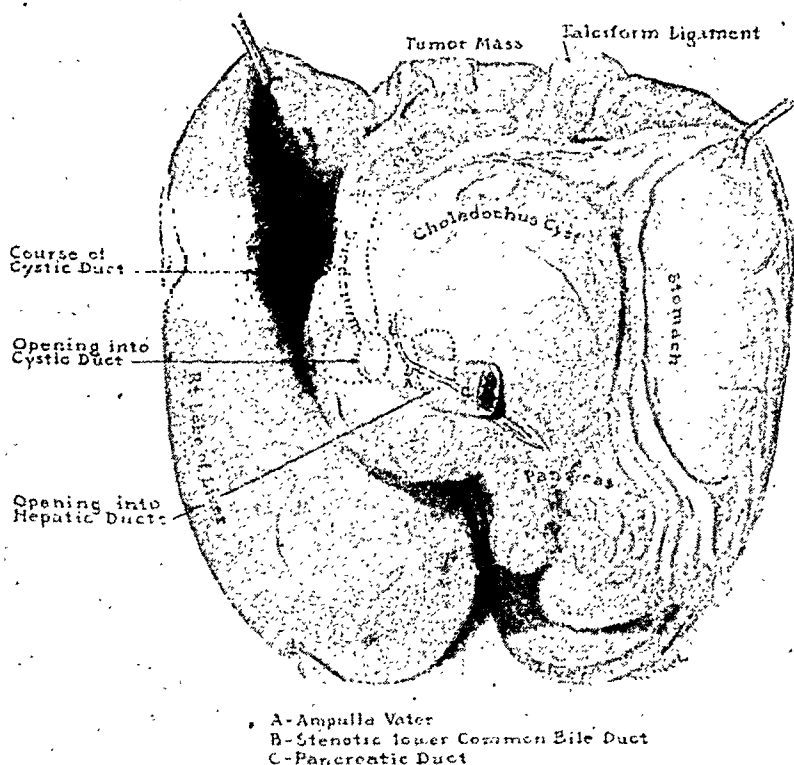


FIG. 2. Inferior view of liver and associated structures showing relations of the cholechochus cyst.

inner lining of the cyst adjacent to the second portion of the duodenum. A probe could be passed through this into a 3 cm. tract where it emerged through the Ampulla of Vater into the duodenum. After this tract was opened, another duct was observed coming in from the mass of pancreas. This duct was patent and opened into the upper portion of the relatively narrow stem of the dilated common duct just outside the large cyst wall. The gall-bladder wall was thick, friable, yellow-white in color, and fungating in character. The size of the organ was normal, and its mucosa showed no areas of ulceration. The cystic duct leading to the dilated common duct was dilated to about 12 mm. in diameter with walls 3 to 4 mm. thick (figure 3).

*Spleen.* This was enlarged weighing 350 gm. Its consistency was soft, and its capsule was covered with fibrin.

*Pancreas.* This was removed with the liver and associated structures. It was flattened and intimately related to the wall of the cystic common bile duct. The ducts were not abnormal. Around the tail was a small rim of tumor tissue.

*Adrenals, kidneys, ureters, bladder and internal genitalia.* Grossly normal.

*Microscopic Examination: Heart and aorta* were normal.

*Lungs* (figure 4 a). The endothelial-lined subpleural lymphatics were filled with clumps and strands of irregular sized and shaped cells which were quite large. Their cytoplasm was eosinophilic and granular. The nuclei were large, spherical to ovoid in shape, with irregularly distributed chromatin. Many mitotic figures were seen as

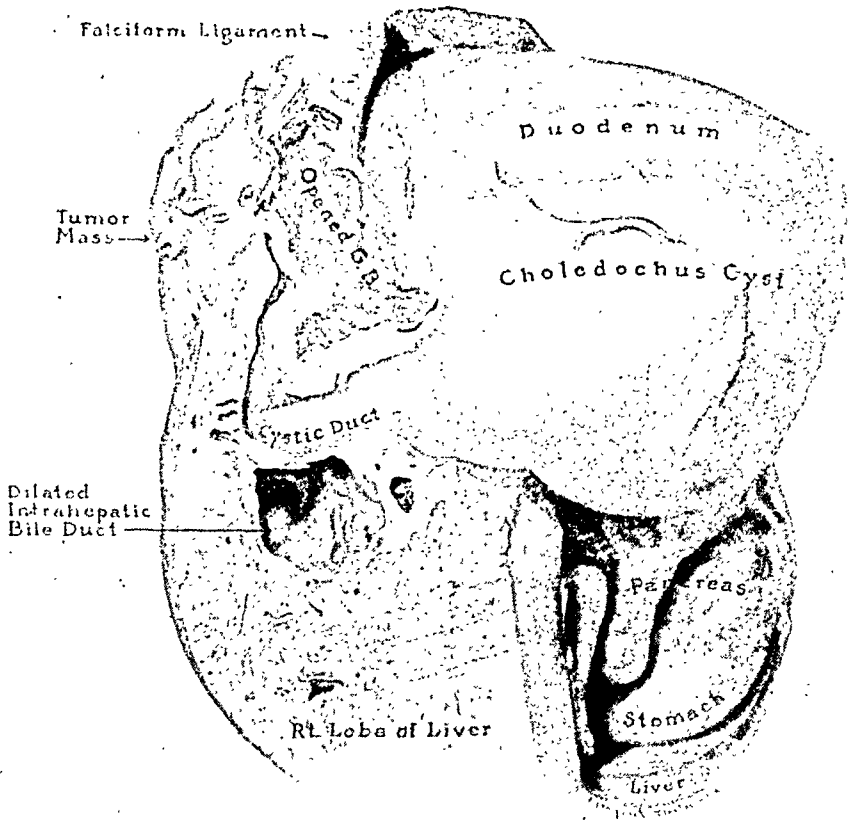


FIG. 3. Right lateral view of the sectioned liver showing the relations of the choledochus cyst, dilated cystic duct, and opened gall-bladder. Note the dilated intrahepatic bile duct.

well as a few multinucleated tumor cells. Similar tumor cells were seen distending alveoli and bronchi. Scattered throughout the neoplastic tissue and thickened alveolar walls were numerous polymorphonuclear leukocytes and lymphocytes. Occasionally a single bizarre shaped tumor cell with a mitotic nuclear figure was seen free in the lumen of a distended blood vessel. Alveoli not distended with tumor cells were filled with granular pink-staining amorphous material and large mononucleated cells. Hilar and paratracheal lymph node sections revealed masses of tumor cells similar to those seen in the lungs. In some regions central necrotic cellular debris was seen, and occasionally the tumor cells occurred in very small clumps which greatly resembled bile canaliculi. These were surrounded by dense collagenous connective tissue which was



FIG. 4 a. Microscopic section (120 X) through edge of right lung showing tumor cells in the subpleural lymphatics on the right and tumor tissue distending alveoli on the left.



infiltrated with lymphocytes, plasma cells, and an occasional eosinophile. No evidence of secretory activity was seen in these tumor cells.

*Gastrointestinal tract.* The subserosal layers were thickened with connective tissue proliferation. Lymphocytes, plasma cells, and clumps of tumor cells were also noted. The serosa was layered with a few areas of fibrinopurulent exudate, and it showed in other areas hyperplastic serosal cells. An omental nodule showed a wild growth of tumor cells.

*Liver* (figure 4b). Over the capsule were numerous nodules of fibrous tissue in which clumps of tumor cells were seen. The central portions were mostly necrotic. Around the nodules were accumulations of plasma cells and lymphocytes. The liver parenchyma was almost entirely replaced by wildly growing tumor cells with some fibroblastic proliferation through it. The tumor seemed to be more predominant in the portal areas. Many central veins were partially or totally occluded by well laminated thrombi with early organization. Large areas of hepatic necrosis infiltrated with polymorphonuclear leukocytes were seen in some places. In other regions there was intercellular edema of the liver cells. An occasional dilated columnar epithelially lined channel was observed and was thought to be a dilated biliary duct.

*Gall-bladder.* The mucosa contained many large lipoid-laden mononuclear cells as well as clumps of tumor cells. The muscular layer was hypertrophied and infiltrated with neoplastic cells. In addition to tumor cells the subserosa contained lymphocytes, plasma cells, and fibrin.

*Cystic common duct.* A few patches of pseudostratified columnar mucus-secreting epithelial cells lined the cyst. Its wall was formed by a dense thick zone of hyalinized connective tissue.

*Spleen.* The capsule and trabeculae were normal. The sinusoids were distended with many red blood cells and collections of polymorphonuclear leukocytes. The lymphoid follicles were normal.

*Pancreas.* The overlying serosa showed the peritoneal reaction and tumor implantation previously described under gastrointestinal tract. There was moderate inter- and intralobular fibrosis with lymphocytic and plasma cell infiltration. The acini were dilated as were a few ducts. Many of the latter were obstructed with polymorphonuclear leukocytes. A few areas of fat necrosis were seen.

*Adrenals.* Aside from acutely engorged blood vessels and a moderate amount of pericapsular hemorrhage, these glands were not unusual.

*Kidneys.* The convoluted tubular epithelium showed marked cloudy swelling, but no other abnormalities were seen.

*Urinary bladder, prostate, and testicle.* These all appeared normal.

Final Diagnoses: 1. Idiopathic dilatation of the common bile duct. 2. Carcinoma, probably hepatic in origin, with extension to peritoneum, omentum, liver, and gall-bladder and with metastases to lungs and tracheobronchial lymph nodes. 3. Acute splenitis. 4. Acute and chronic pancreatitis. 5. Fat necrosis of pancreas.

## DISCUSSION

Idiopathic or congenital dilatation of the common bile duct is a condition of uncertain etiology. Zininger and Cash<sup>1</sup> reported 82 cases in the literature up to 1932, and Shallow, Eger, and Wagner<sup>2</sup> more recently added 93 cases, making a total of 175 cases up to 1943. Though a long list of possible etiological factors has been proposed, that of Yotuyanagi<sup>3</sup> seems to be most widely accepted at the present time. His theory which is based on accepted embryologic studies explains choledochus cyst formation quite satisfactorily. He believes that cystic dilatation of the common bile duct may be due to an unequal rate of epithelial cell proliferation at the stage when the primitive choledochus is still a solid mass.<sup>4</sup>

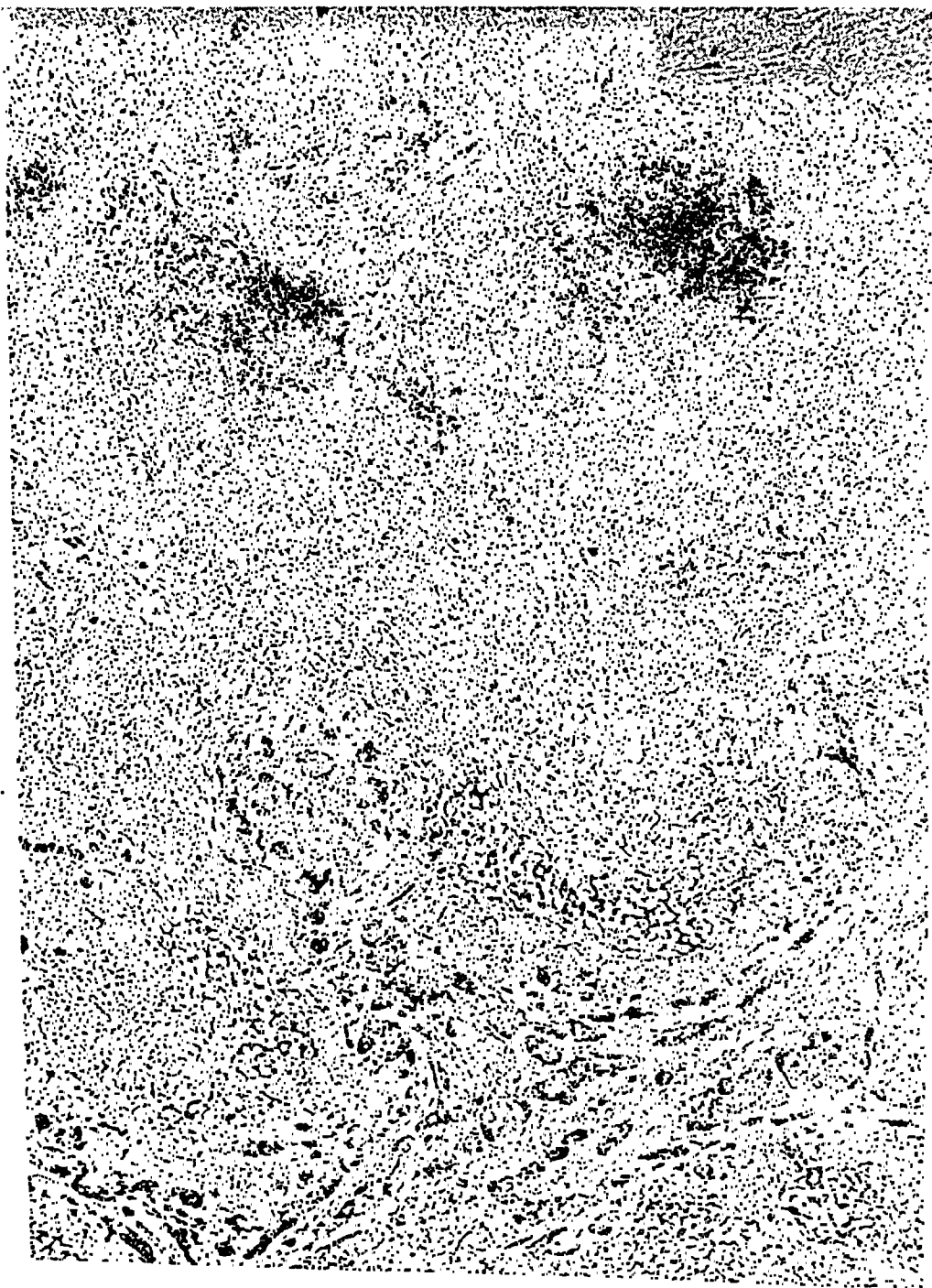


FIG. 4b. Low-power section (40  $\times$ ) of liver showing tumor tissue growing in the portal spaces and areas of hepatic necrosis.

Thus, if there is an increase in proliferation of the cells of the upper portion of the common duct anlage during the stage of physiologic occlusion, and a diminished proliferation in the lower portion at the same stage, when recanalization occurs at a later stage, the upper portion of the duct will be abnormally large and the lower portion relatively small. In the case reviewed in this paper one wonders how great a part increase in pressure in the biliary tract due to the stenotic lower end of the common bile duct played in ballooning out the upper cystic portion.

In this case the presence of a choledochus cyst was not suspected during life. Though the patient had repeated episodes of jaundice since early childhood, he had but a single attack of upper abdominal pain and no palpable subhepatic mass on physical examination. Apparently the downward enlargement of the hepatic lobes was sufficient to prevent the palpation of the dilated common duct. According to the analysis of Shallow, Eger, and Wagner the diagnostic triad in their 175 cases was as follows:

1. Right upper abdominal tumor (77 per cent of their cases)
2. Recurrent bouts of jaundice (70 per cent)
3. Associated abdominal pain (59 per cent)

The correct diagnosis was made or suspected in only 22 or 12.6 per cent of the cases. The disease seems to be essentially one of childhood and early adulthood,<sup>5</sup> and it is more prevalent in the female sex.

Obstruction of the normal flow of bile into the small intestine produces variable changes in the biliary tree and in the liver. Apparently these changes are not uniform and depend on the degree and the length of time of obstruction. Associated anatomic factors found with choledochus cysts usually cause some degree of obstruction. In this case there was a marked dilatation of the major intrahepatic biliary ducts, the hepatic ducts, and the cystic duct together with gross thickening of their walls. The liver was edematous, had numerous areas of focal necrosis, had a certain degree of cirrhotic change, and had malignant tumor tissue growing in it.

It is the latter fact which is of particular interest because of its rarity. Even when unassociated with cystic dilatation of the common bile duct, malignant hepatomata are very uncommon in the white race, especially in the younger age groups. In this case it was not possible to say definitely whether the neoplasm arose in the liver parenchyma itself or in the biliary tree. The histological type of cell present in the tumor was not characteristic, but in some areas of metastases the tumor cells occurred in very small orderly clumps which greatly resembled bile canaliculi. Ewing<sup>6</sup> states that though typical liver-cell tumors and typical bile-duct neoplasms cannot be readily confused, there are still many structures of uncertain significance resulting probably from a growth derived from both of these elements. Therefore, an intermediate group of mixed epithelial hepatic tumors is in evidence. Moreover, according to Ewing some cases of homogeneous type, and evidently single origin, are so far removed from the usual morphology that doubt must remain regarding their true origin.

It seems reasonable that if this patient had not had a choledochus cyst with resultant changes in his biliary tract and liver, he would probably not have developed a malignancy. That a damaged liver, and especially cirrhosis of the liver, can commonly be the precursor of malignant change is a well known fact.

The genesis of the cirrhosis in this case is in accord with the long list of agents and diseases which are known to cause cirrhotic livers and later cancer. This includes chronic biliary disease and biliary obstruction, amebiasis, intrahepatic lithiasis, helminthic infestations, syphilis, hemochromatosis, and various ingested toxins including alcohol. According to Berman<sup>7</sup> who reported 25 cases of primary carcinoma of the liver all of whom had a coexistent cirrhosis of the liver, there may be a racial and sexual susceptibility to hepatic malignancy. His cases were of the Bantu races of South Africa who consume alcoholic beverages from early childhood, but natives of the East Indies and Japan also have an unusually high incidence of carcinoma of the liver. Vint,<sup>8</sup> in analyzing malignant disease in the natives of Kenya, found that 13 per cent of epithelial tumors were primary liver carcinomata which were more common than carcinoma of all other organs including the stomach.

The mechanism by which hepatic cirrhosis causes hepatic cancer is not known, but chronic irritation of the liver tissue is thought to produce cellular proliferation and hyperplasia which may be the precursor of cancer.<sup>9</sup> Berman states that adenomatous hepatic tissue arises in an attempt to compensate for destroyed liver parenchyma. Later the adenomata may undergo malignant degeneration. Steiner<sup>10</sup> attempted to determine the incidence of carcinogenic factor in normal and abnormal (cirrhotic) livers in white people and negroes by injecting extracts of these livers into susceptible animals. All showed about the same incidence of carcinogenic factor for these animals by this method.

The difficulty in diagnosis of this case is apparent from the protocol. Though at first a diagnosis of hypertrophic biliary cirrhosis seemed to fit the clinical picture best, on readmission because of a rapidly growing mass on the anterior surface of the liver, malignancy was suspected, possibly primary locally. In view of the rapid onset and progression of the respiratory symptoms and the pulmonary findings, it was thought that the patient had contracted an extensive pneumonia secondary to his debilitated condition. The fact that supportive therapy including sulfadiazine in adequate amounts and oxygen had no effect whatsoever upon the pulmonary symptoms and signs did not alter this diagnosis. At autopsy the massive infiltration of both lungs with tumor tissue and the lack of pneumonitis were striking. Such a metastatic spread must have appeared with great speed and was probably the immediate cause of death.

The prognosis of congenital cystic dilatation of the common bile duct without operation (anastomosis of the cystic common duct to the duodenum) is usually bad. If early clinical recognition of the disease and proper surgical treatment were carried out, undoubtedly the secondary hepatic changes and in this case neoplastic degeneration could have been delayed or prevented. McWhorter's<sup>11</sup> case lived 13 years in relatively good health after such treatment was carried out.

#### SUMMARY

1. A case of congenital dilatation of the common bile duct with associated primary hepatic malignancy is presented with autopsy observations.

2. The difficulty in diagnosis is emphasized as is also the importance of clinical recognition and proper surgical treatment early in the course of the disease.

3. The likelihood that the biliary obstruction by the choledochus cyst in this case was the precursor of the malignancy is discussed.

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## EDITORIAL

### *PRIMARY ATYPICAL PNEUMONIA*

THIS disease syndrome has occurred so frequently during the past few years that its clinical manifestations are generally known and usually recognized, at least in outspoken cases. Not only has it been frequent in the civilian population, but in the armed forces it has been a major problem, from the standpoint of loss of man power apparently more serious than the bacterial pneumonias.

Knowledge as to the etiology of the disease has not kept pace. Failure to demonstrate any bacterial agent led many investigators to suspect that a virus was concerned, and a number of attempts to isolate a virus have been reported. Some of these earlier investigations have already been reviewed in this journal.<sup>1</sup> Such studies have been handicapped by the fact that all the usual laboratory animals thus far tested are completely or relatively insensitive to the agent. By carrying out serial inoculations, however, in species of animals which seemed to be relatively susceptible, such as the mongoose, the cotton rat and the hamster, several workers succeeded in establishing infections which were caused by some filtrable agent. In some cases the agent was neutralized by serum from human patients convalescent from atypical pneumonia, although not by serum obtained during the acute stage of the disease. All of these experiments are open to grave objections. Of these, the most serious is the possibility that when a series of animals is used, the agent in the sputum may be contaminated or confused with one of the viruses which cause respiratory infections in these animals under natural conditions. Such an infection may be present in an animal in latent form and be activated so as to cause manifest lesions by the manipulations involved in the inoculation. Although attempts were made to exclude such errors, none of these earlier 'viruses' can be regarded as established.

More recently Eaton, Meiklejohn and van Herick<sup>2</sup> have reported the production of pulmonary lesions after primary intranasal inoculation of sputum in cotton rats and hamsters, which, however, could not be reproduced by serial passages. The lesions consisted of scattered areas of consolidation, small or medium in size, which did not cause death of the animal. They also reported establishing the infection in chick embryos by inoculating into the amniotic cavity filtered sputum or unfiltered sterile lung tissue from human cases of primary atypical pneumonia. This was maintained in the embryos by serial inoculation. No definite abnormalities could be observed in these embryos, however, and the presence of the agent could be demon-

<sup>1</sup> Editorial: The etiology of primary atypical pneumonia, *Ann. Int. Med.*, 1944, xx, 145-149.

<sup>2</sup> EATON, M. D., MEIKLEJOHN, G., and VAN HERICK, W.: Studies on the etiology of atypical pneumonia. A filterable agent transmissible to cotton rats, hamsters and chick embryos, *Jr. Exper. Med.*, 1944, lxxix, 649-667.

strated only by intranasal inoculation of hamsters or cotton rats with suspensions of the lungs, trachea and amniotic membranes of infected embryos. This produced consolidations in the lungs identical with those observed in animals inoculated with sputum. The isolation and propagation of the virus in chick embryos removes the risk of contamination with other viruses while the agent is being passed through a series of animals, but it does not eliminate the possibility of activating some latent respiratory virus in the (single) test animal.

In the case of hamsters, which proved to be the more susceptible species, difficulty at first was often encountered because of the presence of a virus, the 'pneumonia virus of hamsters,' antigenically related to the pneumonia virus of mice. This they apparently eliminated by a preliminary immunization of the hamsters with their own virus, which protected them effectively from this but caused no evident change in susceptibility to the agent of primary atypical pneumonia.

Another obvious objection is that in many animals the lesions are not so conspicuous or distinctive as is to be desired.

That these lesions were not due to some latent respiratory virus was shown, they thought, by the fact that of 970 animals inoculated with infected tissues, 59 per cent showed pulmonary lesions, whereas these were recorded in only 2.24 per cent of 357 controls receiving similar uninfected material.<sup>3</sup> Assuming that the observations were accurately and impartially recorded, the chance that this is a coincidence is very small.

The agent was relatively labile. It could be kept active for long periods if preserved in sealed glass tubes at  $-70^{\circ}$  C. At ordinary temperatures it rapidly became inert. It was filtrable through collodion membranes of pore diameters which suggested a size of about 180 to 250 m $\mu$ .

As further evidence of the etiologic significance of the agent, they report experiments showing that it is neutralized by the serum of patients convalescent from atypical pneumonia.<sup>4</sup> Of 69 cases in which serum was obtained both during the acute stage and in convalescence, 61 per cent showed a fourfold or greater (up to sixty-fourfold) increase in titer of neutralizing antibodies. Either no neutralizing power or no increase in titer was demonstrable in the serum of 15 cases convalescent from pneumonia caused by other agents (nine by influenza A, six by bacteria, eight by viruses of the psittacosis group). The serum from convalescent cases of atypical pneumonia showed no protective power (or no increase in titer) for the viruses naturally occurring in these animals.

Further evidence that primary atypical pneumonia is caused by a virus (in the sense of a filter-passing pathogenic agent which is capable of multi-

<sup>3</sup> EATON, M. D., MEIKLEJOHN, G., VAN HERICK, W., and COREY, M.: Studies on the etiology of primary atypical pneumonia. II. Properties of the virus isolated and propagated in chick embryos, Jr. *Exper. Med.*, 1945, lxxxii, 317-328.

<sup>4</sup> EATON, M. D., VAN HERICK, W., and MEIKLEJOHN, G.: Studies on the etiology of primary atypical pneumonia. III. Specific neutralization of the virus by human serum, Jr. *Exper. Med.*, 1945, lxxxii, 329-342.

plication) is furnished by experiments with human volunteers carried out by the Commission on Acute Respiratory Diseases of the U. S. Army.<sup>5, 6</sup> In the first series, 12 volunteers were inoculated with pooled unfiltered sputum and throat washings from several characteristic cases of primary atypical pneumonia. Of these, 10 developed symptoms of respiratory infection after about a week, of which three showed characteristic symptoms of primary atypical pneumonia of moderate severity with roentgenographic changes in the lungs. The others showed only a mild illness. In a second series, sputum and throat washings from six of these men experimentally infected were employed in a group of 42 volunteers. Of 12 who received unfiltered material, three developed the typical disease and five showed minor respiratory illness. Of 12 who received filtered material, again three suffered a typical attack of the disease and five a minor respiratory illness. Of 18 who received autoclaved material, only one showed evidence of a minor respiratory infection.

The occurrence of mild respiratory infections in these groups of inoculated volunteers in association with cases having demonstrable pneumonia lends support to the view expressed by a number of previous observers that pneumonia is only an occasional manifestation of infection with this agent. It seems probable that in many, perhaps a substantial majority of the cases, it causes only an infection of the upper respiratory passages or a bronchitis which clinically can not be distinguished with any certainty from ordinary 'influenza' or the common cold.

Further evidence supporting this view is found in a report by Breslow<sup>7</sup> of an epidemic of a respiratory infection occurring in a grade school in a small town in Minnesota. Of 186 children in the school, 117 contracted the infection during a two month period. In addition, 74 other cases occurred in the town, 41 of which were secondary cases in members of the households of the infected children. A large majority of the cases had mild infections and received no medical treatment. The relatively small number of severer cases closely resembled atypical pneumonia in its milder form as described by other observers. In five of seven of the severer cases examined, evidence of pneumonia was found in roentgenograms of the chest.

Influenza and ornithosis (psittacosis) were excluded by serological tests. Sera from seven of the severer cases were then submitted to Eaton who tested their power to neutralize the virus he had isolated from cases of primary atypical pneumonia.<sup>4</sup> In five cases the titer of neutralizing antibodies in the convalescent serum was four times (or more) greater than in the serum during the acute stage; in one it showed a two-fold increase, and in one both specimens showed a high titer. It seems, therefore, that the agent

<sup>5</sup> Commission on Acute Respiratory Diseases: An experimental attempt to transmit primary atypical pneumonia in human volunteers, Jr. Clin. Invest., 1945, xxiv, 175-188.

<sup>6</sup> Ibid.: Transmission of primary atypical pneumonia to human volunteers, Jr. Am. Med. Assoc., 1945, cxxvii, 146-149.

<sup>7</sup> BRESLOW, L.: Epidemic of acute respiratory disease associated with atypical pneumonia, Jr. Clin. Invest., 1945, xxiv, 775-779.



concerned in these cases was serologically identical with the virus isolated by Eaton et al. Unfortunately none of the milder cases was tested in this way, but the epidemiological evidence strongly suggests that many of them, at least, were caused by the same agent.

Although the evidence reviewed is not entirely conclusive, this work strongly suggests that a substantial proportion of the cases of primary atypical pneumonia are caused by a specific virus which appears to be different from any previously reported. It is quite possible that other cases, clinically similar, may be caused by viruses which are antigenically different, as has been shown in the case of influenza. It is also highly probable that the infection produced by this agent may vary from a mild disease resembling a common cold to a severe illness with extensive pulmonary lesions. It is manifestly one of the most important of the common respiratory infections.

## REVIEWS

*The Specificity of Serological Reactions.* Revised Edition. By KARL LANDSTEINER, M.D. The Rockefeller Institute for Medical Research. 310 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Mass. Price, \$5.00.

The text of the revised edition was completed by Dr. Landsteiner before his untimely death in June 1943, and was prepared for publication by E. K. Landsteiner. The book follows the form of the earlier edition but the material has been brought up to date. Owing to the war, recent foreign material, except the British, was not available for review.

Following the introduction which outlines immunological phenomena and gives the general nomenclature, there are two chapters devoted to the serological specificity of proteins and to cell antigens. This is followed by a section on artificially prepared conjugated antigens and the reaction of simple chemical cellular substances is then presented.

The volume concludes with a chapter by Dr. Linus Pauling entitled "Molecular Structure and Intermolecular Forces."

The book bears the mark of an outstanding investigator and will remain a classic contribution to this field of investigation.

M. A. A.

*Textbook of Obstetrics.* By HENRICUS J. STANDER, M.D., F.A.C.S. 1287 pages; 25 × 17 cm. 1945. D. Appleton-Century Co., New York. Price, \$10.00.

This edition represents the Ninth Edition of "Williams' Obstetrics," the first six of which were written by the late Dr. J. Whitridge Williams. This is the first edition of this work which appears directly under the name of Dr. Stander, who is Professor of Obstetrics and Gynecology in the Cornell University Medical College.

The author of this textbook for students and practitioners states in his preface that the art and science of obstetrics as taught in the Cornell University Medical College and practised in the New York Lying-In Hospital are presented.

The general plan of the work is similar to the previous editions, but the arrangement is different in that the subjects are presented in sections and sub-sections rather than in chapters. The publishers state that the book has been revised, rewritten and reillustrated.

In complying with wartime standards reducing the bulk of paper, a welcome reduction in the size of the book has been accomplished. The type is clear and readable. There are 973 splendid illustrations on 740 figures, many of which are new and many are in color. Ten sections and 49 sub-sections cover the field of obstetrics. Historical and many of the theoretical considerations appear in small type. Although the bibliography at the end of the sections and sub-sections is quite extensive, one could wish that more of the modern references had been included.

The author's style of writing is clear and forceful, but because of the magnitude of the scope, and the multiple references and statistical data appearing in the text, it is the belief of the undersigned that some of the effectiveness as a book primarily for students thereby has been lost.

No mention is made of the various clinical uses of Willett's forceps such as in the treatment of certain types of placenta previa. Insufflation of the vagina is advocated.

as a method of treatment of trichomonas vaginalis vaginitis during pregnancy, but the possible dangers of such a mode of treatment during pregnancy are not pointed out. No reference is made to the use of the newer anti-malarial drugs in the treatment of malaria during pregnancy.

Despite these factors, this textbook is a complete and modern presentation of the conservative practise of obstetrics in the New York Lying-In Hospital, and undoubtedly will remain among the classics in its field.

J. E. S.

*Penicillin in the Treatment of Infections.* By CHESTER S. KEEFER, M.D. and DONALD G. ANDERSON, M.D. 48 pages; 15 × 18 cm. 1945. Oxford University Press, New York.

In view of the rapid advances being made in chemotherapy, especially in the use of antibiotics, it is impossible for any one monograph to keep abreast of the developments in the field. However, this concise yet inclusive volume presents in a well-organized discussion the information necessary for the intelligent clinical use of penicillin.

The history, characteristics and pharmacology of the substance are considered briefly, followed by a more detailed discussion of its clinical uses in the more common infections. The toxic reactions are included in an interesting presentation and a bibliography containing 109 references emphasizes the intense study that has been under way in this field.

The data here accumulated confirm the authors' statement in the final paragraph that penicillin "is without doubt the most effective agent for the treatment of infectious diseases ever discovered."

J. Z. B.

### BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*An Introduction to Essential Hypertension.* By RICHARD F. HERNDON, M.D., F.A.C.P. 88 pages; 23 × 14.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$2.50.

*Dr. W. C. Roentgen.* By OTTO GLASSER, Cleveland Clinic Foundation. 169 pages; 22 × 14.5 cm. 1945. Charles C. Thomas, Springfield, Ill.

*Roentgen Diagnosis of Diseases of the Gastrointestinal Tract.* By JOHN T. FARREL, JR., M.D., Clinical Professor of Radiology, Graduate School of Medicine, University of Pennsylvania. 271 pages; 23.5 × 15.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$5.50.

*Preventive Medicine and Public Health.* By WILSON G. SMILLIE, A.B., M.D., D.P.H., Sc.D. (Hon.). 607 pages; 22 × 14.5 cm. 1946. The Macmillan Company, New York. Price, \$6.00.

*Digitalis and Other Cardiotonic Drugs.* By ELI RODIN MOVITT, M.D. 204 pages; 24.5 × 16 cm. 1946. Oxford University Press, New York.

*Neurosyphilis*. By H. HOUSTON MERRITT, A.B., M.A., M.D., RAYMOND D. ADAMS, M.A., M.D., and HARRY C. SOLOMON, B.S., M.D. 443 pages; 24 × 16 cm. 1946. Oxford University Press, New York.

*Science and Scientists in the Netherlands Indies*. Edited by PIETER HONIG, Ph.D., and FRANS VERDOORN, Ph.D. 491 pages; 27 × 18 cm. 1945. Board for the Netherlands Indies, Surinam and Curacao, New York City. Price, \$4.00.

*Convulsive Disorders*. Edited by RUCKER CLEVELAND, Ph.D. 83 pages; 25.5 × 18 cm. 1945. Research Laboratories and The Department of Clinical Investigation of Parke, Davis and Company.

## PHILADELPHIA AND AMERICAN MEDICINE

THE approaching twenty-seventh Annual Session of the American College of Physicians, to be held in Philadelphia, May 13-17, 1946, will bring the members of this College back to the cradle of organized medicine in this country. If a cradle were all that the city of Philadelphia had to offer the visiting physician, it is obvious that the meetings would, in all probability, have been scheduled elsewhere. The truth is, that today Philadelphia's physicians welcome their colleagues not to a city of the past, but to one into which the destiny which broods over cities has breathed a timeless and unquestioned devotion—that towards the art of medicine.

Philadelphia, in size the third city of the country, vies with Chicago for first place in the number of recognized medical schools, each having five.



DEPARTMENT OF MEDICINE.

East side of Fifth Street, between Library and Walnut Streets, 1765-1766. (Building known as Surgeons' Hall.)

Anatomical Hall—Philadelphia 1765  
Cradle of American Medical Education.

The statistics on hospitals and physicians in the three cities are approximately in proportion to their population.

*The Medical School of the University of Pennsylvania* \* in September of this year will undertake for the one hundred and eighty-first year to offer organized medical instruction to the youth of this and other lands. The record is unique in this country. This first medical school in the colonies came into being in 1765 as the Department of Medicine of the College of Philadelphia, largely through the efforts of a distinguished Philadelphia physician, John Morgan, who, appropriately, was elected to the first medical professorship in the colonies. Morgan belonged to that great group of Philadelphia physicians whose superb vigor of mind and body, and whose devotion to the progress of American medicine, left their impress indelibly upon the face and in the soul of the city.

On June 21, 1768, ten students walked out of the commencement exercises of the College of Philadelphia (now the University of Pennsylvania), with the first medical degrees granted by the first medical school in the country. Since that day, approximately 18,000 other youths have followed in their footsteps.

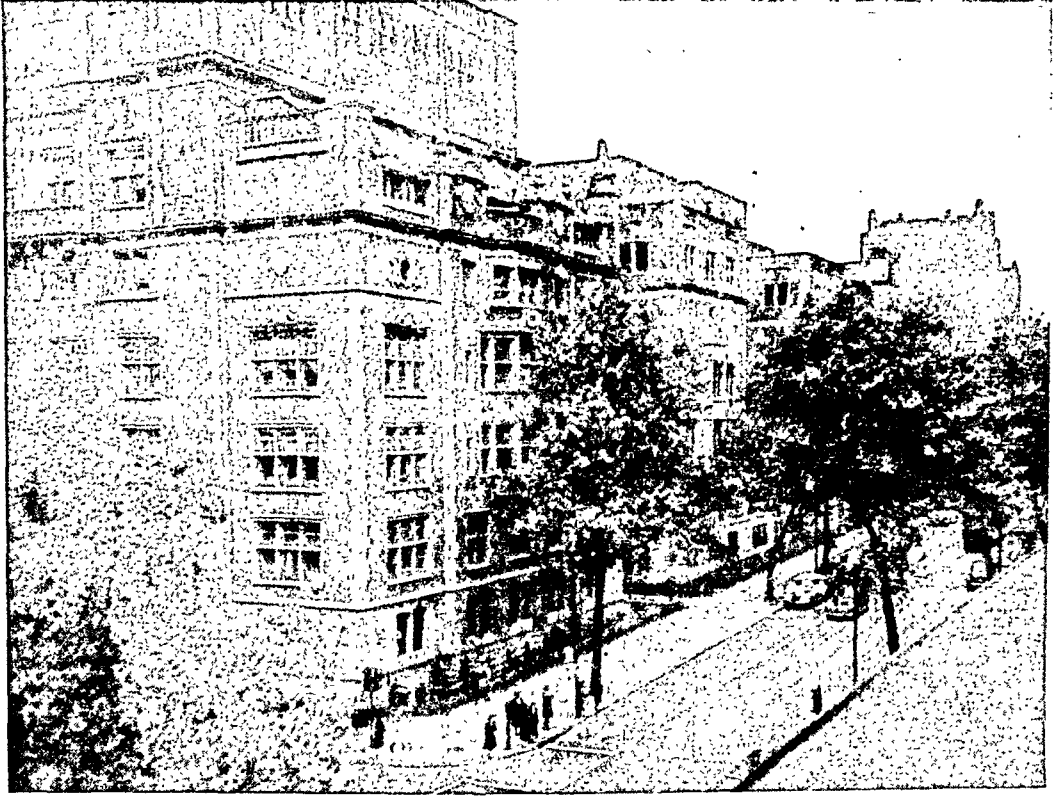
The buildings that have housed the Medical School have been several; the catalogue of professors is long and illustrious. Over the earlier homes it would not be profitable at this time to pause. From the list of professors, piety and affection demand that we single out at least the names of William Shippen, Jr., Benjamin Rush, James Woodhouse, Benjamin Smith Barton, Caspar Wistar, Nathaniel Chapman, Philip Syng Physick, William P. Dewees, William Edmonds Horner, Robert Hare, George B. Wood, Hugh Lenox Hodge, Joseph Leidy, D. Hayes Agnew, William Goodell, William Pepper, Alfred Stille, William Osler, Richard A. F. Penrose, H. C. Wood, Leonard Pearson, C. L. Leonard, John Ashhurst, George W. Norris, Louis Duhring, J. William White, George A. Piersol, E. T. Reichert, John Marshall, James Tyson, John H. Musser, John G. Clark, Edward Martin, Alfred Stengel, Barton C. Hirst, John B. Deaver, George E. de Schweinitz, Charles K. Mills, William G. Spiller and Charles H. Frazier.

In 1873 the University moved to its present location in West Philadelphia adjoining the grounds of the Philadelphia General Hospital. The University Hospital was erected on the campus at that time. The Laboratory of Hygiene was built in 1892, and the Laboratories of Pathology, Physiology, and Pharmacology were formally opened in 1904. In 1928, however, there was attached to their building a splendid five-story structure which now houses the Departments of Anatomy, Physiological Chemistry, Research Surgery, and the Anatomy Department of the Graduate School of Medicine.

In the same year, work was begun on the Maloney Pavilion. This ten-story building at Thirty-Sixth and Spruce Streets connects with the Hospital

\* The following material has been assembled and in large part taken verbatim from the Reports and Announcements and from individual histories of the various institutions.

and furnishes quarters for the William Pepper Laboratory of Clinical Medicine (originally this laboratory occupied a building erected for it in 1894, the first unit of its kind in the country), the John H. Musser Department of Research Medicine, the Eldridge R. Johnson Foundation for Medical Physics, the Department of Physical Medicine and the George S. Cox Medical Research Institute, various special diagnostic clinics of the Medical Out-Patient Department, and about 25 private rooms.



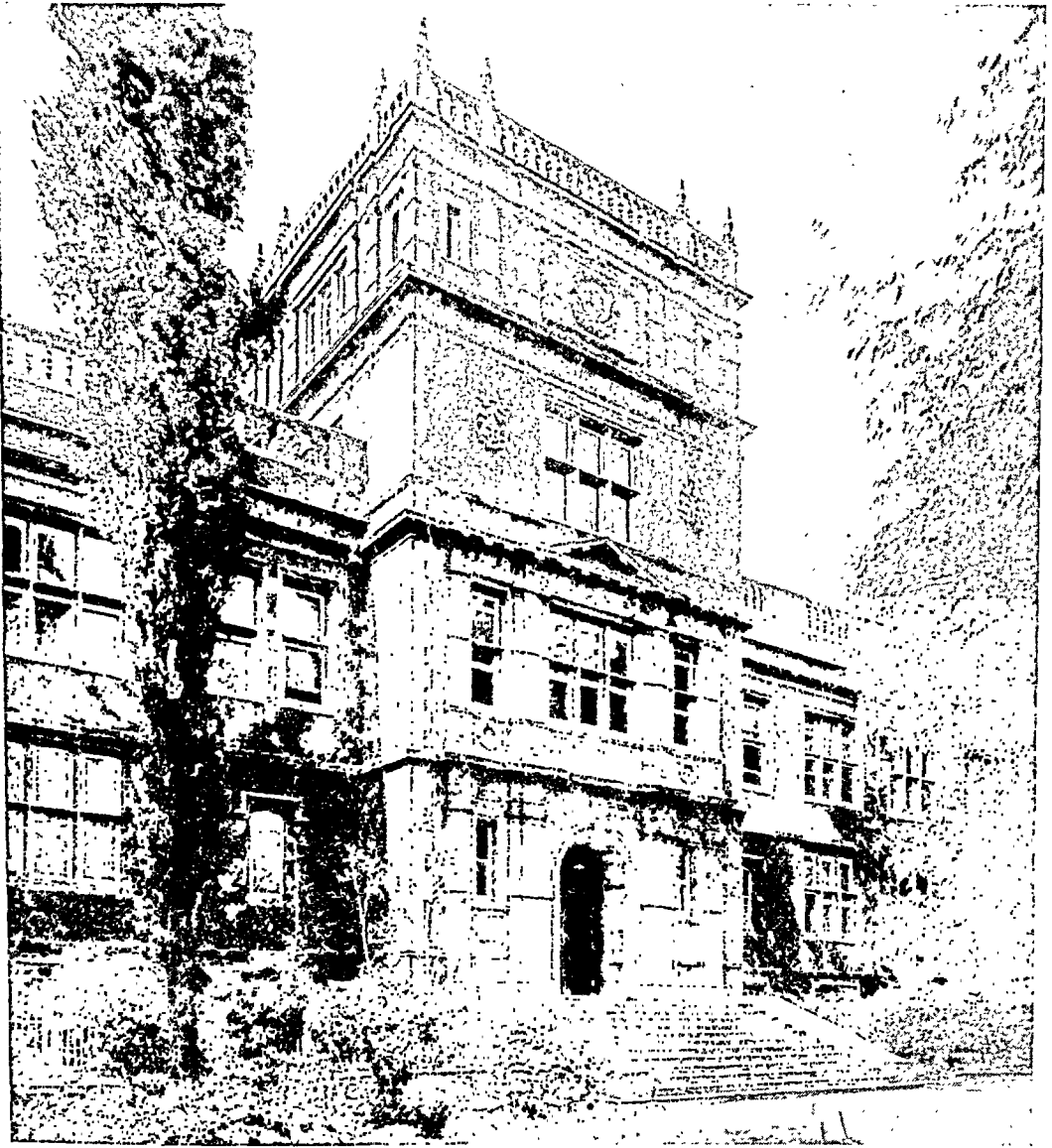
Hospital of the University of Pennsylvania.

The Wistar Institute of Anatomy and Biology, at Thirty-Sixth Street and Woodland Avenue, incorporated in 1892, was the first American University Institute devoted to advanced study and research in anatomy and biology. The Henry Phipps Institute for the study, treatment, and prevention of tuberculosis, at Seventh and Lombard Streets, was established in 1903, the first fully organized and equipped institution of the kind with University connection.

Other notable "firsts" of which the School of Medicine is entitled to boast include the graduate courses in public health leading to the degree of Doctor of Public Health; a separate building for research in, and the teaching of, hygiene; the Department of Research Medicine whose members devote practically their entire time to investigation.

The School includes in addition to the Research Foundations mentioned above, the Robinette Foundation, the Gynceean Hospital Institute of Gynecologic Research, and the Laboratory of Dermatological Research.

The University Hospital, which is an integral part of the School, and whose staff is drawn entirely from members of the medical faculty, was the



Main Entrance to Medical Laboratories, University of Pennsylvania.

first in the country to be built by a university for the use of its medical school. Several years ago the Neurologic Institute of the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases was merged with the University Hospital and housed in a four-story building on the hospital grounds. There are at present available a total of 729 beds. During the



fiscal year of 1944 to 1945, there were 16,073 hospital admissions, 115,399 visits to the out-patient departments, and 11,383 surgical operations were performed. Students of all four classes are taught here every clinical subject.

This medical school, in brief, in the course of 181 years of active life has met with amazing resource and courage the demands of our increasingly complex civilization, so that today its equipment enables it to offer its students every advantage of theoretical, practical, and research study. Age has indeed not withered, nor custom been allowed to stale.



Graduate Hospital of the University of Pennsylvania.

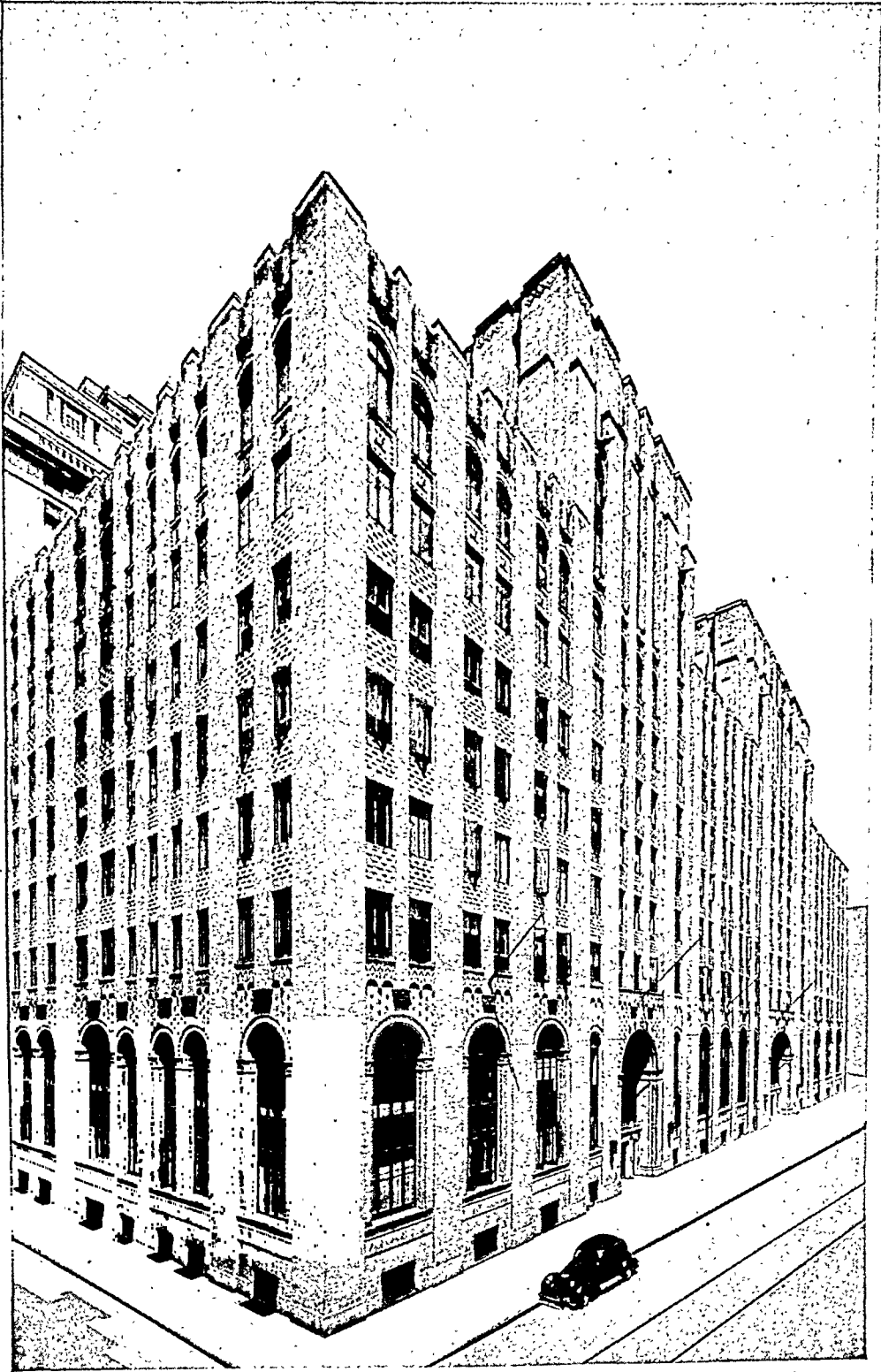
The University's Graduate School of Medicine, located at Nineteenth and Lombard Streets, was organized in 1916 by a merger between the University and the old Medico-Chirurgical College of Philadelphia, which had

been founded in 1881. In 1918 the Philadelphia Polyclinic and College for Graduates in Medicine merged with the Graduate School of Medicine and formed the Polyclinic Section. Later additions of assets included the Diagnostic and Howard Hospitals, and the North American Sanitarium.

The Graduate School of Medicine today is, administratively, a separate university unit, or association of units, operating in complete coöperation with the School of Medicine, and, like the latter, is administered ultimately by the University's vice-president in charge of medical affairs and its Board of Trustees. The students of the Graduate School are suitably qualified physicians who after a basic year of formal systematic training may become, substantially, clinical or research assistants to members of the faculty throughout the city, intramurally and extramurally, or to carefully selected physicians in other communities. The essential feature of the Graduate School's "Pennsylvania Plan" of graduate medical education is the upbuilding of an extensive coöperation between the central organization, that is, the Graduate School, and extramural medical organizations and their staffs. At present, 50 of Philadelphia's medical organizations are found to be thus coöperating. The Graduate Hospital, covering more than one city block, with a capacity of 461 beds, is the clinical teaching center of the school. During the year 1944-45, its activity rate was 68,861 bed days, 4,128 operative cases, and 79,004 out-patient visits. The Graduate School of Medicine of the University of Pennsylvania is today the only institution of its kind in Philadelphia.

*Jefferson College and Hospital.* Philadelphia's second medical college, in point of time, is an equally vigorous ancient of the second generation. This is the Jefferson Medical College, founded in 1825, as the Medical Department of the Jefferson College of Canonsburg, Pennsylvania. Its first class was graduated in the following year. In the intervening 120 years, it has conferred a medical degree upon approximately 17,500 of its students.

The College today occupies a handsome building on Walnut Street, just west of the old College building at Tenth and Walnut Streets where now is situated its Curtis Clinic. The College building, opened in 1929, represents, like the Maloney Pavilion of the University of Pennsylvania, a thoroughly modern response to the technical developments of the day as they affect the equipment for medical instruction and research. Herein are contained, in addition to administrative offices, professors' rooms, work rooms, recitation, lecture, demonstration, and assembly rooms, laboratories large and small, for the use of the various departments, a library, and the College Museum. More recently an additional floor in the College Building has been completed as a fully equipped modern Department of Pharmacology. At present an entire floor is under completion for offices and research laboratories for the Departments of Experimental Medicine, Experimental Surgery, Neuropathology and Neurosurgery. In 1941, the Cardeza Foundation for Research on Diseases of the Blood and Allied Conditions was organized. This Foundation now operates the Transfusion-Plasma



Jefferson Hospital.

Unit, Photographic Biologic Laboratory and Research Laboratories of the Staff. A modern air-conditioned animal house and operating rooms have also been completed.

The clinical teaching is today carried on largely in the College's Hospital, adjacent to the College itself. This building, opened in 1907, has a capacity of 475 ward beds, in addition to 272 for private and semi-private patients, and offers every facility for this purpose. Under the supervision of professors and experienced instructors, students are required to participate in operations and to assist in the administration of anesthetics. When the interests of the patient are not thereby jeopardized, the student may follow the case from admission to discharge.

The Curtis Clinic, adjoining the College, and conforming to it architecturally, is the out-patient unit. The building is planned so as to group the various medical, surgical, and specialty divisions. The Hospital's central location insures an exceptionally large service demand, particularly in the out-patient department. The surgical division of the Jefferson Hospital performed 8,593 operations in the year ending May 31, 1945. For the same period there were 63,062 admissions to the various departments of the Hospital and the total out-patient service amounted to 195,697 visits.

In 1924, the Samuel Gustine Thompson Annex to the Jefferson Hospital was opened. This building contains the teaching clinical amphitheater, seating 550, a maternity department, bronchoscopic wards, and a teaching clinical laboratory upon the roof. The Department of Anatomy, including Descriptive and Practical Anatomy, Histology and Embryology, and Anatomy as applied to Medicine and Surgery, is housed in a building of its own at Clinton and Eleventh Streets, a few blocks from the College. This is the Daniel Baugh Institute of Anatomy, containing laboratories, a museum, amphitheatres, and a notable departmental anatomical reference library. The Department for Diseases of the Chest is likewise set apart, in a building at 238 Pine Street. Although the activities here are concerned largely with the problem of tuberculosis, other related conditions are studied and treated. Twelve students are selected from the fourth year class to reside in the department and assist in the preparation of histories and in the special study of patients.

Jefferson's faculties, which weathered severe storms in the early days, have contained some of the most distinguished Philadelphia physicians of national reputation: such men, for instance, as George McClellan, John Eberle, Daniel Drake, Nathan R. Smith, Robley Dunglison, Joseph Pancoast, J. K. Mitchell, Thomas D. Mütter, Charles D. Meigs, Franklin Bache, Samuel D. Gross, Samuel H. Dickson, Robert E. Rogers, the younger Gross, J. M. DaCosta, Roberts Bartholow, W. W. Keen, Hobart Amory Hare, James Wilson, Edward P. Davis, and J. C. DaCosta. The College's history is a colorful one, and its achievements loom large in the history of the city's and the nation's medical life.

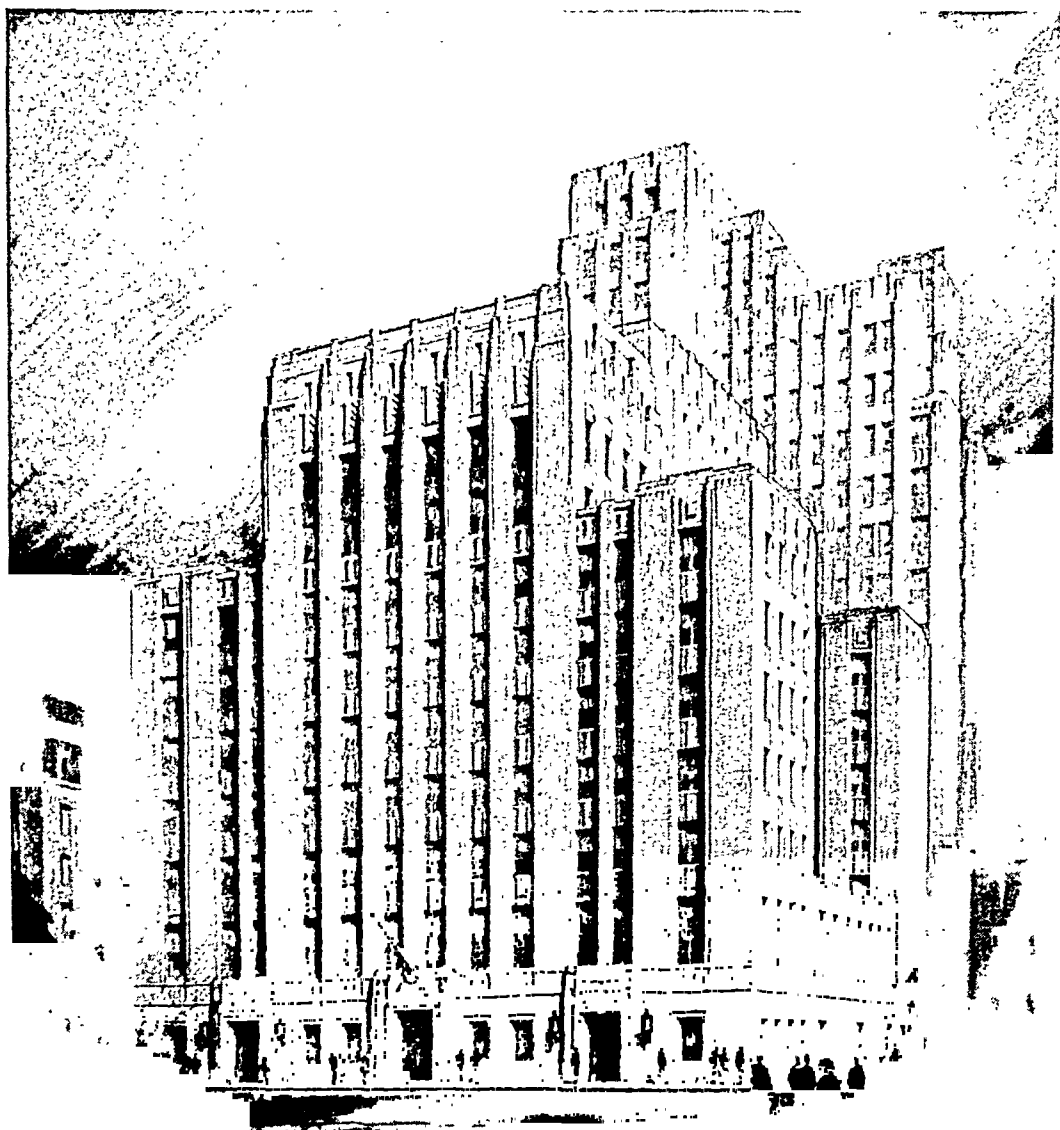
*Hahnemann Medical College and Hospital.* In 1845, homeopathy had practitioners (about 250 in number) in 22 states, but no institution where homeopathy was taught. Its doctrine, in fact, was promulgated under a cloud of disapproval by the medical profession, which culminated in resolutions passed, in 1847, by the newly formed American Medical Association, tending to stigmatize it as irregular. It was in an attempt to gain legal recognition for the system that the Homeopathic Medical College of Pennsylvania, the oldest of its kind in the world, was founded in 1848. In 1869, this college was consolidated with the Hahnemann Medical College of Philadelphia under the corporate name of the Hahnemann Medical College of Philadelphia, and in 1885 the corporation of the Hahnemann Medical College and Hospital of Philadelphia was brought by merger into existence and located at its present site.

With admirable sincerity of purpose the College has pursued its course, constantly strengthening its base and widening its curriculum in line with the developments in the fields of medicine. Its requirements today include two years of college work as a minimum, preference being given those applicants with more preparation. The Medical School offers a standard four years' course, and confers upon its graduates, by provision of its state charter, two degrees, those of Doctor of Medicine and Doctor of Homeopathic Medicine. Although special attention is given to *Materia Medica* and Therapeutics and to the principles of Hahnemann, Hering, Dunham, and other noted men in the field, the prime object of the school is to give a broad and thorough medical education. This it successfully achieves.

The College building contains lecture rooms, a large library and museum, laboratories, rooms for operative surgery and practical obstetrics, the administrative and faculty offices and reading rooms. The College Library may be divided into two departments. One contains about 15,000 volumes and is especially of historical interest. Here are found Dr. Hering's notable collection of the writings of Paracelsus, Dr. A. R. Thomas' collection of very old and rare anatomical books, all of Hahnemann's works in the original and the most complete library of homeopathic literature in existence. The other constitutes a valuable working library and reading room for students and contains a file of the principal medical and scientific journals. Investigation in medical literature is considered an essential part of the college course.

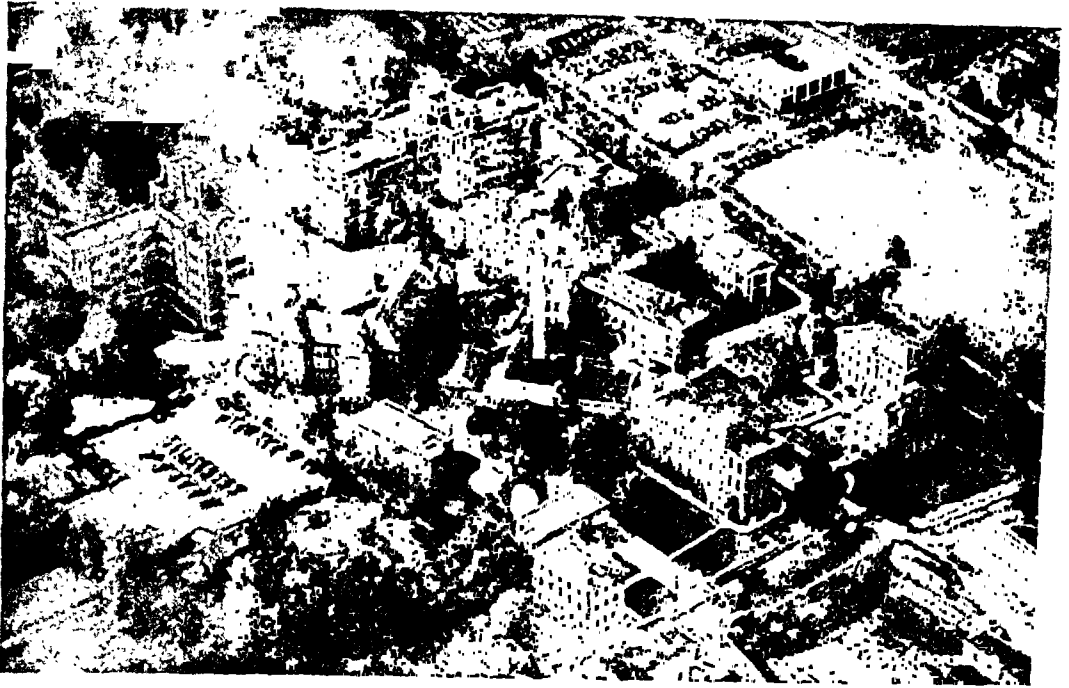
The new Hahnemann Hospital, 20 floors in height, was opened in 1928 and has a total capacity of 700 beds, 370 of which are public. Over 12,000 bed patients are treated in a year, and an average of over 125,000 visits are made to the out-patient department. The Hospital is equipped with electrocardiographic, fluoroscopic, basal metabolism and clinical laboratories. The arrangements are such that the operating units are coördinated on the same floor with the roentgenological department, the clinical and pathological laboratories of the Hospital being on the floor directly below. As

with the other schools and hospitals which we have mentioned, the faculty of the School and the staff of the Hospital are one, and the clinical material presented by the Hospital is directly available for teaching purposes and is used constantly.



Hahnemann Medical College and Hospital.

The tendency of the day in this country is unquestionably toward greater uniformity in medical instruction, and to the advance along this line Hahnemann College has devoted itself with obvious success.



Jewish Hospital.

*Woman's Medical College of Pennsylvania.* The position of women in American medicine would probably be as uncomfortably anomalous today as it was in the early years of our national life, had there not come quietly into existence in 1850, in Philadelphia, an institution quaintly called, in the terminology of the day, the Female Medical College of Pennsylvania. This was the first college in the world regularly organized for the medical education of women, and it is still the only medical school in the United States exclusively for women.

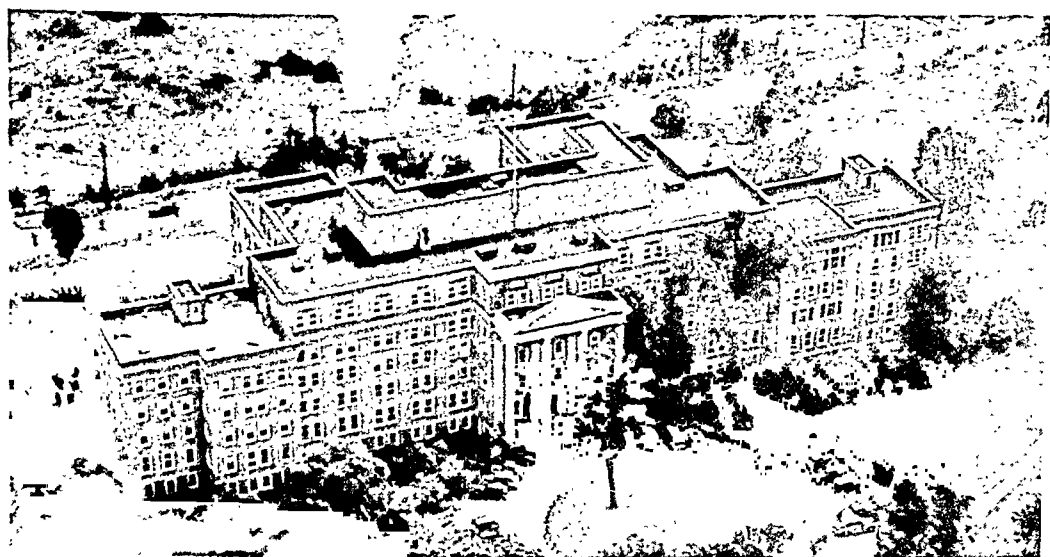
The opening session of the College found 40 students enrolled for instruction by a faculty of six, all men. The first class graduated numbered eight, of whom one, Dr. Ann Preston, was soon elected to the Chair of Physiology and Hygiene, the first woman to have a place on the faculty. Today, well over two-thirds of the faculty are women.

It was to be expected that the problem of adequate clinical instruction would be a difficult one for the pioneers to overcome, and such indeed it was. In 1860, we find the first official reference to the founding of the Woman's Hospital of Philadelphia. A lack of foresight in the acquisition of its charter, however, led to a situation in which the College and the Hospital came under the management of dual groups, which hindered the use of the Hospital for clinical teaching. Fortunately, other clinical opportunities were opening up. On January 2, 1869, the distinguished Alfred Stille prefaced his lectures in the amphitheater of the Philadelphia Hospital with these words:

"Ladies and Gentlemen: I have pleasure in meeting you today. It is the first time in my medical experience that I have had the opportunity of

addressing women among the audience of my pupils. We are sometimes shocked at what is novel, simply because it gives us an unaccustomed impression, but in the present instance I must say that, so far as I am personally concerned, I not only have no objection to seeing ladies among a medical audience, but, on the other hand, I welcome them."

In 1869, likewise, the Board of Managers of the Pennsylvania Hospital came nobly to the rescue with an invitation to the women students to attend the clinical lectures at that institution. On November 6 of that year about 30 women students accepted the invitation, but presumably somewhat to their chagrin. The novelty was not only a shock to the male students of the Pennsylvania Hospital, but it was received with conduct on their part which quickly made of the incident a *cause célèbre*. The way of the pioneer, which is, in a sense, that of the transgressor, was ever hard.



Woman's Medical College.

The site and buildings of the present College and Hospital, opened in 1930 and occupying approximately 10 acres, present the former Female College of Pennsylvania, under its present title, as one of Philadelphia's distinguished medical institutions. The Hospital, containing 152 beds and 21 bassinets, is conducted by the Corporation under the professional direction of the faculty. A fully equipped heart clinic was opened in 1932 and a bronchoscopic clinic in 1933 to 1934. An out-patient clinic is conducted at Barton Dispensary, 1309 North Twenty-Second Street, as well as at the Hospital. The students today enjoy the extramural privileges, such as the use of the Libraries of the College of Physicians and the Academy of Natural Sciences, and of various clinics, accorded their male colleagues. Much of their clinical teaching is now conducted in the wards and clinics of the Philadelphia General Hospital, the Woman's Hospital, the Memorial Hos-



pital at Roxborough, the Pennsylvania Hospital and its Institute for Nervous Diseases, St. Christopher's Hospital, and the Philadelphia Hospital for Contagious Diseases. If the millennium has not yet been attained, that is a circumstance of which we are all, men as well as women, in one way or another the victims. Certainly, the work of the Woman's Medical College of Pennsylvania has contributed not a little toward defining the road forward.

*Temple University School of Medicine.* The Medical Department of Temple University was opened in 1901. It is, therefore, the youngest of Philadelphia's five recognized medical schools. No one, however, with even a bowing acquaintance with the country's medical schools will be deceived by that fact. Its status today as one of our major schools of medicine is uncontested. This position it has achieved in comparatively few years through its success in drawing to it a distinguished faculty and in furnishing them and their students with the most modern equipment for research and instruction. Its success in attracting medical students may be gauged by the fact that, though the first-year class is limited to 100, well over 2,000 applicants are considered annually by the Committee on Admissions.

If the annals of this school are as yet too brief to provide a historian's field-day, it should at least be pointed out that the Temple University School of Medicine was the first coeducational medical school to be established



Temple University Medical School and Hospital.

in Pennsylvania. Its third graduating class, in fact, included two women. Thus far at least had we traveled since the embattled days of '69.

The present building occupied by the School was opened in 1930. It is situated on Broad and Ontario Streets, directly opposite the University's Hospital. Dispensaries and administrative offices share with the library the first and second floors. The various departments are housed in the third to sixth floors, while the seventh contains medical and research rooms and storage facilities for mammals, rodents, etc.

The Temple University Hospital, where most of the clinical teaching is done, is directly under the control of the faculty. It ranks with the larger institutions of its kind in the city in facilities and equipment, having a bed capacity of 469, which affords abundant material for every branch of clinical instruction. A laboratory building on the hospital grounds provides a well equipped clinical laboratory, an autopsy room, private laboratories for original research, and rooms for teaching purposes.

Temple University itself, founded in 1884 by Russell H. Conwell, celebrates this year its sixty-second anniversary. The seal of the University bears the motto *Perseverantia vincit*. As one looks at the achievements of its medical school in so short a period as forty-five years, one is almost tempted to believe that perseverance, soon or late, if the object be a fair one, does win.

*Philadelphia College of Pharmacy and Science.* It would certainly not be fitting to close this brief survey of Philadelphia medical schools without recalling to the visitor's attention the fact that the Philadelphia College of Pharmacy and Science, at Forty-Third and Kingsessing Avenue, today one of the leading institutions of its kind in the country, was also the first college of pharmacy in the new world. The history of this college, founded in 1821, in Carpenter's Hall, seat of the Provincial Assembly and of the first general Congress of the Colonies, covers practically the history of pharmaceutical education in this country. Its founding, by 68 druggists and apothecaries bent upon education by the masters of their craft, indicates once more the early and deep devotion of Philadelphia's medical groups to the highest development of their science. And it is by way of illustrating the high quality of instruction which has always been maintained in the College that we recall as members of its faculties George B. Wood, Joseph Carson, Franklin Bache (great-grandson of Benjamin Franklin), Robert Bridges, William Proctor, John M. M. Maisch, Samuel P. Sadtler, and Joseph P. Remington.

*Hospitals.* The hospitals which are directly connected with the various schools of medicine have already been briefly mentioned. We may be forgiven under the circumstances if from the many others we select for a brief introduction those which will be the most intimately involved in the forthcoming meetings.

*The Pennsylvania Hospital.* To those who have the fortune to see medicine in its historical perspective, the Pennsylvania Hospital is perhaps more than any other medical institution in the country a rich source of

pleasure. One of the largest and most important hospitals in the city today, it yet retains both in its exterior and in its interior much that is evocative of its long and notable past. It is, in fact, the oldest hospital in the United States which was intended wholly for the sick and wounded and which has continued on its ancient site and maintained its original name.



Pennsylvania Hospital.

The founding of this Hospital was predominantly the work of Benjamin Franklin and his close friend, the physician, Thomas Bond. The latter is remembered today also as the originator of the Bond splint for the treatment of fractures of the forearm, and for the invention also of an instrument for extracting foreign bodies from the esophagus, thus inaugurating what seems to have become an old Philadelphia custom.

The roster of the Hospital has always contained the names of many of the city's leading physicians—the Bonds, Morgan, Shippen, Jones, Rush, Physick, James, Parish, Otto, Ward, Pepper, Gerhard, Agnew, Packard, Ashhurst, Meigs, Harte, Stengel. This gratuitous service was instituted by the Hospital's first physicians. It is estimated that the services performed by the Staff today are worth well over \$500,000 a year.

The present divisions of the Pennsylvania Hospital are the Department for the Sick and Injured, the Department for Mental and Nervous Diseases, and the Institute of the Pennsylvania Hospital. The Philadelphia Dispensary, founded in 1786, is now also carried on as part of the "Out-Patient Department of the Pennsylvania Hospital and Philadelphia Dispensary."

The Department for the Sick and Injured, at Eighth between Spruce and Pine Streets, occupies the site it first moved to in 1756. An interesting analysis of its service, given in one of the Hospital's recent Annual Reports, indicates that during the year there was an application for either emergency

or ward care every 14 minutes; a ward bed or a private room received a new patient every 84 minutes; the Out-Patient Department cared for a patient every three and two-fifths minutes; the police patrols brought a patient to the door every five hours and 22 minutes; a surgeon performed an operation every two hours and four minutes. No further words are needed to show that this Department of the Hospital, which, like the Jefferson College Hospital, is in the center of the city, fulfills the extraordinary demands made upon it as courageously as it did in the days when it was a new institution in a New World.

The Department for Mental and Nervous Diseases and the Institute are reminders that the Pennsylvania Hospital from its origin was the pioneer in the Colonies in the treatment of the mentally unstable not as criminals but as patients suffering with mental disease, subject to individual treatment and eventual return to reason. This department was moved to its site in West Philadelphia, at Forty-Fourth and Market Streets, in 1841, and its first Superintendent, Dr. T. S. Kirkbride, so impressed his personality upon the institution that, for many years, it was familiarly known as "Kirkbride's." The treatment of its more than 200 patients is naturally on an individual basis, planned after a comprehensive study of the patient, and employs such methods, depending on the diagnosis, as fever, occupational and physiotherapy, the Aschner treatment, music, recreation, etc.



Institute of the Pennsylvania Hospital.

The Institute, at Forty-Ninth and Market Streets, represents the Hospital's latest development in the line of treating mental conditions. The keynote of its work is that of prevention of mental and nervous illness. Here in quiet and comfortable surroundings the attempt is made to solve the emotional problems as much as possible by natural means under medical direc-

tion. Civic recognition of the work of the Institute was signalized in 1933, by the presentation of the Philadelphia Award to the Chief of Clinical Service and Medical Director of the Institute. The career of the Pennsylvania Hospital has been memorable in many ways, in none other perhaps so memorable as in its steady devotion to the understanding and healing of the mentally sick and injured.

*Philadelphia General Hospital.* The Philadelphia Almshouse was erected in 1731 or 1732. In 1835, it officially adopted the title "Philadelphia Hospital," which again gave way, in 1902, to the title it bears today, namely, "Philadelphia General Hospital."

The history of this institution from its earliest days as an alms—or "bettering" house, receiving, in the older fashion, the poor, the sick, and the lunatic, to its position today as the largest hospital in the city and one of the largest in the country, forms one of the more remarkable chapters in the history of medicine in Philadelphia.

Though the title "Philadelphia Hospital" was not adopted until 1835, there is ample evidence that a hospital department existed at the Almshouse from its early days. And the title adopted in 1835 was again curiously inconclusive in that the Almshouse and the Hospital continued to be located together at the present site of the Philadelphia General Hospital until 1920, when the Almshouse was removed to separate quarters away from the hospital grounds.

The earliest records of the Hospital, unfortunately not so well preserved as those of the Pennsylvania Hospital, show that the pre-Revolutionary attending physicians numbered many of the famous group so intimately connected with the founding and the early days of the Pennsylvania Hospital and the Medical School of the present University of Pennsylvania. Since those days the staff of the Hospital has included at one time or another Philip Syng Physick, Caspar Wistar, Benjamin Smith Barton, Nathaniel Chapman, T. C. James, Hugh Lenox Hodge, S. D. Gross, D. Hayes Agnew, William Osler (whose notable postmortem work was done here), S. Weir Mitchell, J. H. Musser, H. C. Wood, Louis A. Duhring, W. W. Gerhard (it was in this Hospital that he made his clinical observations on the differentiation of typhus from typhoid fever), Alfred Stengel, William Hughes, Joseph Sailer, David Riesman, DeForest Willard, and others of equal prominence.

When the Hospital moved, in 1834, to its present site and thereafter assumed the name "Philadelphia Hospital," it assumed unofficially the name "Blockley," from the township in which it was placed, and this was the name by which it was commonly known, to which it still occasionally answers today. In 1834, it was supposed to accommodate 400 sick, 200 more, if necessary, and was difficult of access from the medical schools. Today it has a capacity of about 3,000 beds and has as its near neighbor the Medical School of the University of Pennsylvania.

The greatest strides in the new Philadelphia General Hospital have been

taken in the last 15 years. This period has seen the development of the outpatient clinics to which well over 60,000 visits are paid each year. Particularly noteworthy is the work being done in cardiology, in metabolism, in occupational diseases, in tuberculosis, in radiology, and in the neuropsychiatric, prenatal, and postnatal clinics. The Saturday morning clinics, for



Philadelphia General Hospital.

the general practitioners of the city, are a prominent feature of the Hospital's life today. Cases of special interest in the Hospital are drawn upon for material and some prominent physician, not necessarily of the staff, is invited to talk upon them.

This period has seen, also, the erection of a building for the adequate housing of the interns and resident physicians, and one for the care of the female tuberculous. The impressive proportions of the Philadelphia General Hospital today, an idea of which can be readily gained from the accompanying aerial view, and the notable work which it continues to do, are further tributes to the vigor and integrity of Philadelphia's medical men who have had occasionally, in making this Hospital possible, severe political battles to wage in order to maintain adequate scientific independence and progress.

*The Children's Hospital.* The Children's Hospital of Philadelphia, at Eighteenth and Bainbridge Streets, in the past year opened another wing (Rush) of its projected final group. This well emphasizes the continuing growth of the country's oldest hospital designed exclusively for children, established in 1855, and the third such hospital in the world. The first home of the Hospital had accommodation for 12 patients; the present Hospital, opened in 1916, has a capacity of 156 beds.

The primary purpose of the Hospital was to care for children suffering from diseases which could not be properly treated in their homes. An interesting commentary on the changes of direction which the progress of medicine takes is the Hospital's Department for Prevention of Disease, inaugurated in 1914, as an outgrowth of a previous Social Service Department. This Department, the first of its kind in any hospital in America

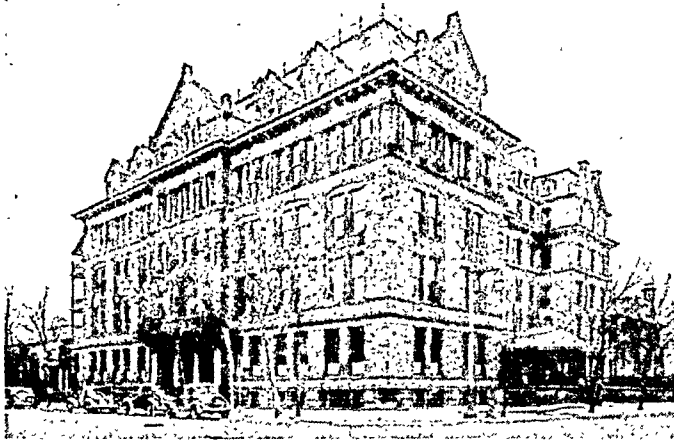


Children's Hospital.

and one which draws visitors from all over the world, treats annually both in their homes and in the clinics well over 100,000 patients. This, in addition to an annual regular out-patient service of over 40,000 visits and an in-patient roll of approximately 3000 patients, is sufficient evidence of the remarkable service which this Hospital gives to the children of Philadelphia. As a further development in the general field of Child Welfare, the Hospital established in 1923, a Child Guidance clinic. This clinic was designed to examine and recommend the right management of problem children, truants, potential criminals, and other misfits. It has under its guidance constantly over 800 of these children. Philadelphia, once again, has proved itself a pioneer in the now accepted doctrine, proposed so early in our medical history by the Pennsylvania Hospital, that the physician cannot exclude from his realm the unsound mind, no matter how sound the body.

*Lankenau Hospital.* The Lankenau Hospital, incorporated in 1860, opened for patients in 1866, as the German Hospital of the City of Philadelphia. Its present name honors its second President, John D. Lankenau, whose personal care and generosity are credited with being the chief agents through which it reached its present standing among the city's hospitals.

Originally designed as a hospital in which the German people of Philadelphia might be treated by physicians and nurses who could speak their native tongue, the Hospital has inevitably come to serve a wider function. Though the Hospital is excellently equipped for its annual in-patient service demand of about 4000 patients and an out-patient visit total of about 37,000, probably its chief interesting feature is its Research Institute. This was built in 1925, by the late Rodman Wanamaker, at the cost of about half a million dollars. The activities of the Clinical Laboratories of this Research Institute include in a year about 60,000 examinations of all types. A Division of Art and Photography records the completion of numerous drawings, photographs, and photomicrographs of patients, specimens, and ap-



Lankenau Hospital.

paratus, which are used for following the progress of patients, for teaching, and for illustrating contributions to medical literature. A filing system allows quick collection of previously completed illustrations of a large variety of subjects. The Out-Patient Departments, the Diagnostic Clinic, and the Maternity Department have profited particularly from the work of the Institute in the ability that it provides to reconstruct early conditions.

The Research Division of the Institute, as is now generally known, has concerned itself with the problem of the chemistry of cell growth, and its researches in the subject of sulphur metabolism have directed attention from many quarters to the work of the Institute and the Hospital of which it is a part.

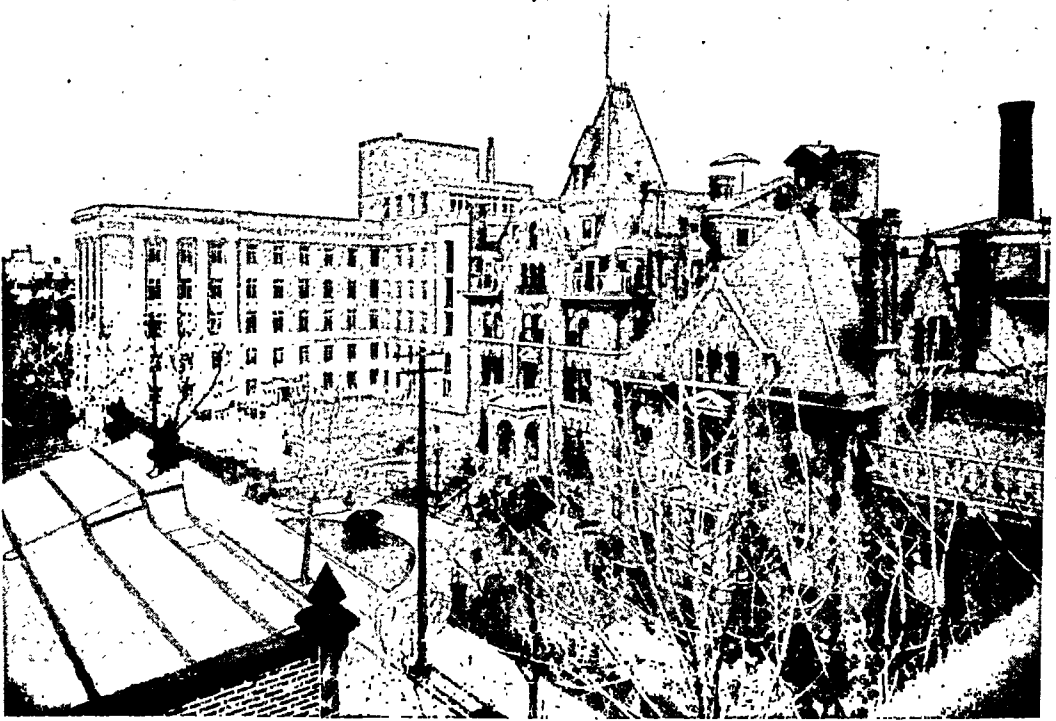
*Presbyterian Hospital.* The Presbyterian Hospital, incorporated in 1871, and opened the following year, was a happy product of the reunion, in 1869, of the two branches of the Presbyterian Church.

This Hospital, which never has had any restrictions as to race, creed, or color, has a consulting and major staff of about 170, and provides beds for 425 patients. The Out-Patient Department, with an annual visit-total of about 63,000, offers clinics in allergy, diseases of the heart, diabetes, thy-



roid and other conditions. A Child Health Clinic follows the Department for Prevention of Disease of the Children's Hospital, in emphasizing the modern doctrine of prevention.

The physicians and interns, as in most hospitals, hold weekly clinical conferences in the laboratory for the discussion of unusual pathological conditions which arise in the routine of observation in the Hospital, and papers and other presentations are delivered at monthly scientific meetings. Recently a research committee has been instituted with a view to extending the general importance of the work done in the Hospital.

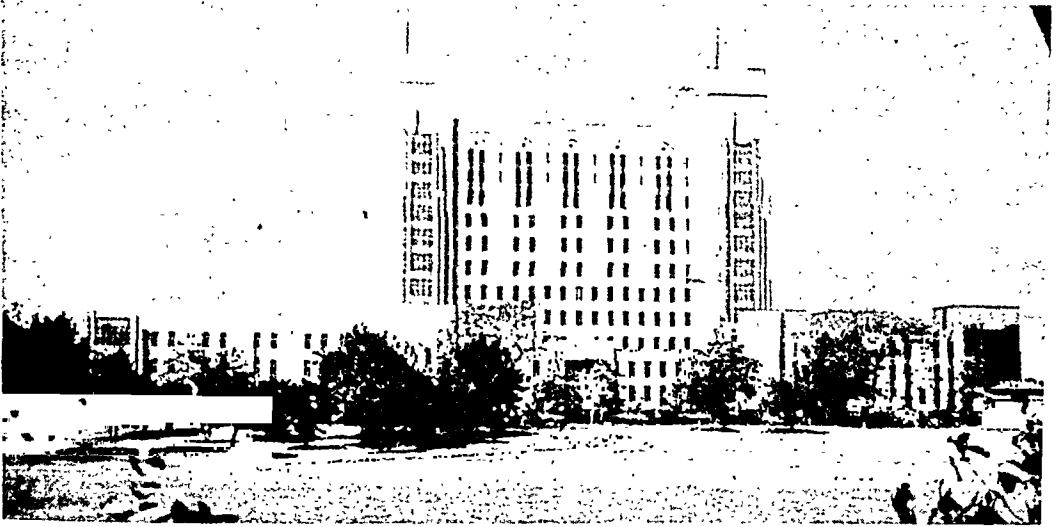


Presbyterian Hospital.

In general, coöperation between the Hospitals and the Medical Schools, at which we have hinted in speaking of the Graduate School of Medicine's "Pennsylvania Plan," is engaged in widely, and there can be little doubt that its ultimate effect is an advantageous one for all concerned.

It is to be expected that a city so rich in medical institutions should be rich alike in medical societies. About 50 of these announce their meetings in the Weekly Roster published by the Philadelphia County Medical Society, and these do not constitute the entire list. Two medical organizations must be mentioned especially. The largest in the city is the Philadelphia County Medical Society, at Twenty-First and Spruce Streets. Organized in 1849 under the presidency of Dr. Samuel Jackson, it has been from the beginning,

an extraordinarily active and effective medical police in the interests of the public welfare. Of late years it has become increasingly active in stimulating the interest of the younger physicians, the interns and medical students, by series of postgraduate seminars and round table discussions held in its building. The Weekly Roster which it publishes is an invaluable guide to the activities of the city's medical societies.

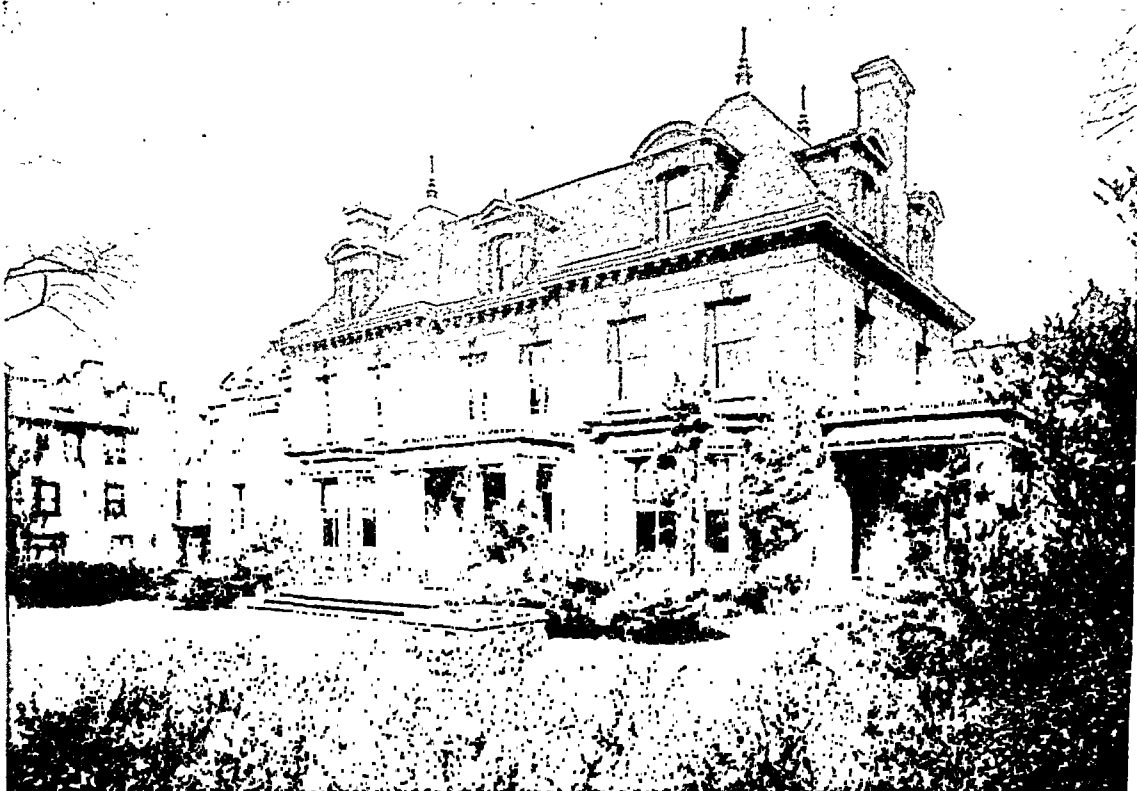


U. S. Naval Hospital.

The oldest existing medical society in Philadelphia, and the most famous, is the College of Physicians, organized in 1787. Its present splendid home, which was built for it and to which it moved in 1909, houses one of the finest medical libraries in the world, both in size and quality. Its collections of medical incunabula and other medical books of the greatest rarity are known in Europe as well as in this country. Over 200 of the incunabula have already been photostated by the Library's photostatic machine and are accessible to scholars in the reading room.\* These collections and one of the most comprehensive files of medical periodicals in the country have resulted in making the College a court of first resource for those working in medical literature. The College holds monthly scientific meetings, except during the summer, often with distinguished guest speakers, and its Fellows have organized five Sections which likewise hold monthly meetings in the lecture halls of the College, which are used also by other medical societies in the city. The College, thus, is open six full days and many evenings in the week, carrying on that "diffusion of medical knowledge" proposed as among its objects by one of its distinguished founders, Benjamin Rush.

\* A special exhibit of some of the rarest items has been arranged for the American College of Physicians and, likewise, arrangements have been made to introduce its members to the Mutter Museum and other treasures in the College building.

Philadelphia's medical activities today include, further, the publication of 19 medical journals. Philadelphia is the home of five of the largest medical publishing houses in the country. Here the headquarters of the American College of Physicians was established in 1926. Philadelphia today teaches



Headquarters, The American College of Physicians, 4200 Pine Street.

medicine, practices medicine, thinks in terms of medical progress with the singular devotion which it inherits and passes on year by year. It is, in a spiritual sense at least, the medical center of America.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

The following Fellows of the College have become Life Members. (Listed in the order of subscription. Subscriptions received up to and including March 14, 1946.)

Dr. Kenelm Winslow Benson, Berkeley, Calif.  
Dr. Paul Veal Ledbetter, Houston, Tex.  
Dr. Henry Nathan Leopold, San Antonio, Tex.  
Dr. Frank Reid Mount, Portland, Ore.  
Dr. Henry Rohnert Carstens, Detroit, Mich.  
Dr. J. Sudler Hood, Clearwater, Fla.  
Dr. Archie Marvin Roberts, Los Angeles, Calif.  
Dr. Eugene Fagan Traut, Oak Park, Ill.  
Dr. Kenneth S. Davis, Los Angeles, Calif.  
Dr. Oscar Benwood Hunter, Washington, D. C.  
Dr. James Burnett Shields, Glens Falls, N. Y.  
Dr. Earl Charles Waterbury, Newburgh, N. Y.  
Dr. Lorenz William Frank, Denver, Colo.  
Dr. Harold Lazarus Tonkin, Williamsport, Pa.  
Dr. William Sullivan Horn, Fort Worth, Tex.  
Dr. William Campbell Blake, Tampa, Fla.  
Dr. Lawrence Chatfield Towne, Lansing, Mich.  
Dr. William R. Vis, Grand Rapids, Mich.  
Dr. William Crane Nichols, Fargo, N. D.  
Dr. Henry Costill Gotshalk, Honolulu, T. H.

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### ALL GOVERNORS OF THE COLLEGE HAVE RETURNED FROM MILITARY SERVICE

During the period of the war several Governors of the College were on active duty with the Medical Corps of the Army and the Navy. We are gratified to report that all have returned to their home states and have now resumed their posts as Governors of the College.

Tribute should be made to those Fellows who accepted the responsibility of Acting Governors during the absence of the regular Governors. Each one performed with enthusiasm and efficiency the duties of Governor and was largely responsible for the maintenance of College activities and College interests in his respective state.

Dr. Thomas M. McMillan was the Acting Governor for Eastern Pennsylvania during the absence of Dr. Edward L. Bortz; Dr. Patrick L. Ledwidge, Detroit, was the Acting Governor for Michigan in the absence of Dr. Douglas Donald; Dr. Edward H. Ryneearson, Rochester, was the Acting Governor for Minnesota during the absence of Dr. Edgar V. Allen; Dr. Ellsworth L. Amidon, Burlington, was the Acting Governor for Vermont during the absence of Dr. Paul K. French; Dr. Edwin G. Bannick, Seattle, was the Acting Governor for Washington during the absence of Dr. Charles E. Watts; Dr. Richard Hawkes, Portland, was the Acting Governor for Maine during the absence of Dr. Eugene H. Drake.

Dr. Wetherbee Fort was for a time Acting Governor for Maryland during the absence of Dr. Louis Krause, and Dr. J. Edwin Wood, Jr., was the Acting Governor

for Virginia during the absence of Dr. Walter B. Martin, but there was one election held during the war when Drs. Fort and Wood were officially elected Governors for their respective states and Dr. Walter B. Martin was elected a member of the Board of Regents.

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COURSE No. 9—A.C.P. POSTGRADUATE PROGRAM—SPRING 1946—THORACIC DISEASES.

Owing to unavoidable circumstances, Dr. John Alexander, Professor of Surgery, at the University of Michigan Medical School will be unable to assume the directorship of Course No. 9—Thoracic Diseases, scheduled to be given at Ann Arbor from May 6-11, 1946. Dr. Alexander's assistant, Dr. Cameron Haight, Associate Professor of Surgery, University of Michigan Medical School has agreed to direct this course for the American College of Physicians.

We regret very much that Dr. Alexander has been forced to withdraw, but we are confident that Dr. Haight will direct this course as ably as would Dr. Alexander. The subject matter remains the same and the schedule has already been announced in the Final Bulletin of Postgraduate Courses for the Spring (page 34). The Thoracic Surgery Staff of the University Hospital and other members of the University of Michigan Medical School Faculty are prepared to carry on in Dr. Alexander's absence. Registration for this course is now open and should be made directly with the College Headquarters Office in Philadelphia.

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COURSE No. 5—A.C.P. POSTGRADUATE PROGRAM—SPRING 1946—NUTRITION.

An intensive, personalized course in "Nutrition and Nutritional Deficiency States" will be directed by Dr. Tom D. Spies at the Nutrition Clinic of the Hillman Hospital in Birmingham, Alabama, for a small group of from 10 to 15 men, beginning June 3 and ending June 8. This course was first announced in the College News Notes in the February number of the Annals of Internal Medicine and has been included in our Final Bulletin of Spring Courses.

The course will be devoted to the various phases of nutrition and nutritional deficiencies in a practical and stimulating manner, including clinics and ward rounds, field studies, and laboratory demonstrations. Deficiency producing diets and therapeutic diets will be stressed. The principles of nutrition and metabolism will be defined, and the diagnosis and treatment of deficiency states will be presented by means of informal discussions and clinics. Nutrition in relation to dentistry, heart failure, and public health will be noted.

Registration is now open and will be limited to a maximum of 15 men. Reservations will be made in the order of their receipt at College Headquarters in Philadelphia. Hotel accommodations will be provided through the courtesy of the Birmingham Chamber of Commerce.

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Dr. Edward de S. Matthews, F.A.C.P., New Orleans, recently retired from the Army and has resumed the practice of internal medicine and cardiology at New Orleans, being associated with Dr. Chaille Jamison, Clinical Professor of Medicine, Emeritus, at Tulane University. Dr. Matthews holds an appointment as Instructor in Medicine at Tulane.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has recently been honored by the Director General of the Republic

of El Salvador, Central America, for proficient scientific work in the field of public health. Dr. Geiger was awarded an honorary degree granting him the title of "Benemérito de la Salubridad Continental."

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Dr. Wann Langston, F.A.C.P., Oklahoma City, Professor of Medicine and Chairman of the Department of Medicine, has been appointed Temporary Dean of the University of Oklahoma School of Medicine.

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Dr. Currier McEwen, F.A.C.P., has returned from military service with the rank of Colonel and with the Bronze Star and the Legion of Merit, and has resumed his duties as Dean of the New York University College of Medicine. In July 1945, Col. McEwen became Chief Consultant in Medicine for the European Theater of Operations with Headquarters in Paris and Frankfurt.

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Dr. Robert P. McCombs, F.A.C.P., formerly of Philadelphia, has recently been separated from the Navy and has assumed the position of Director of the Postgraduate Division and Assistant Professor of Medicine, Tufts College Medical School, with offices at the Joseph H. Pratt Diagnostic Hospital, Boston.

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Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., President of the American College of Physicians and member of the Board of Trustees of the American Medical Association, recently attended a testimonial dinner in Nashville in honor of Dr. Harrison H. Shoulders, President-Elect of the American Medical Association.

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Dr. Wallace M. Yater, F.A.C.P., Washington, has been appointed Associate Editor of the *American Heart Journal*.

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Dr. William H. Leake, F.A.C.P., Beverly Hills, Calif., was named President of the Medical Veterans Organization in that region.

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Col. James O. Gillespie, F.A.C.P., MC, USA, was first reported "missing in action" in the early part of the war. He had been stationed in the Philippines at the time of the final surrender at Corregidor. Later information coming through in 1943 informed us that he was a prisoner of the Japanese. Col. Gillespie was liberated after the fall of Japan and has returned to the United States, his address being, 3444 Divisadero Street, San Francisco, California.

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Capt. John F. McManus, MC, AUS, F.A.C.P., was recently made Chief of Medical Service at the U. S. Army General Hospital, Camp Edwards, Mass. It is anticipated that he may soon be released from active duty and will then return to the practice of internal medicine in Boston.

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Dr. George C. Griffith, F.A.C.P., formerly of Philadelphia, after separation from the Naval Reserve, has opened an office at 117 E. Colorado Street, Pasadena, California, for practice limited to consultation in Cardiovascular Disease.

Dr. Henry S. Houghton, F.A.C.P., who preceding the war was Acting Director of the Peiping Union Medical College, Peiping, China, was held as a political prisoner by the Japanese for the duration of the war, having been released shortly after the middle of August 1945. He returned to this country and is now restored in health and strength. His headquarters is with the Trustees of the Peiping Union Medical College, 49 W. 49th Street, New York City.

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Dr. George N. Barry, F.A.C.P., Oklahoma City, Oklahoma, has been serving in the U. S. Naval Reserve since June 13, 1945, but has not previously been recorded in these columns on active duty. This brings the total number of members of the College serving with the Army, Navy, or Public Health Service to 1982.

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Brigadier General William C. Menninger, F.A.C.P., Director of the Neuropsychiatry Consultants Division, Office of The Surgeon General, has been awarded the Distinguished Service Medal for "solving one of the most serious medical problems faced by the Army" in activating a plan of treatment for neuropsychiatric cases, which restored many thousands of mentally sick men to health and usefulness.

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Lt. Col. Philip T. Knies, MC, F.A.C.P., Army Quarantine Liaison Officer, Preventive Medicine Service, Office of The Surgeon General, has received the Legion of Merit for his work in the "planning, organization, and supervision of the Army foreign quarantine program."

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Dr. F. M. Pottenger, F.A.C.P., Monrovia, California, was recently given signal honor by the Los Angeles County Tuberculosis and Health Association, which presented him with a handsome parchment scroll commending his outstanding leadership in the fight against Tuberculosis. Dr. Pottenger has been elected President Emeritus with "voice and vote on the Board of Directors," of the Los Angeles County Tuberculosis and Health Association.

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The late Dr. Philip H. Pierson, F.A.C.P., has been honored posthumously by the Board of Trustees of the Alum Rock Sanatorium, San Jose, California, who dedicated a gift of \$5000 to a Memorial Medical Research Fund in honor of our former distinguished Fellow. Dr. Pierson, formerly Clinical Professor of Medicine at Stanford University Medical School and consultant at Alum Rock Sanatorium, died unexpectedly on January 17, 1946.

Dr. Harold G. Trimble, F.A.C.P., is Chairman of the Board of Trustees and Dr. B. H. Wardrip, F.A.C.P., is Secretary of the Board of Trustees of Alum Rock Sanatorium.

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For the past month Tulane University of Louisiana School of Medicine, Department of Graduate Medicine, has been conducting review courses in various phases of general medical practice. The program from the middle of April until the end of May is as follows:

April 15-20, Diseases of Nervous System  
April 22-27, Nutritional and Metabolic Diseases  
April 29-May 4, Infectious Diseases  
May 6-11, Neoplastic Diseases  
May 13-18, Obstetrics and Gynecology  
May 20-25, Traumatology

Dr. E. David Sherman, F.A.C.P., Sydney, Nova Scotia, has been appointed Consultant in Medicine to the Department of Veterans Affairs Hospital.

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The Division of Medical Services of the School District of Philadelphia has sponsored a symposium on The Heart and The School Child. The following Fellows of the College, who reside in the city of Philadelphia, took part in this program:

Jacob M. Cahan, M.D., F.A.C.P.  
Alexander Margolies, M.D., F.A.C.P.  
Charles C. Wolferth, M.D., F.A.C.P.  
Ella Roberts, M.D., F.A.C.P.  
Mary H. Easby, M.D., F.A.C.P.  
Geo. Howard Gehrmann, M.D., F.A.C.P.  
Samuel Bellet, M.D., F.A.C.P.  
Carl C. Fischer, M.D., F.A.C.P.

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Lt. E. A. Rasberry, Jr., (MC), USN, has been awarded a Clinical Fellowship in Medicine to begin on or about July 1, 1946. Dr. Rasberry will serve this Fellowship at the Hospital of the University of Pennsylvania, Philadelphia, under the directorship of Dr. T. Grier Miller in the Department of Gastro-enterology.

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Dr. Robert P. Morehead, F.A.C.P., Winston-Salem, N. C., who is Associate Professor of Pathology and Director of that department at the Bowman Gray School of Medicine of Wake Forest College, has been appointed Educational Director of the North Carolina Division of the field army of the American Cancer Society.

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#### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

- Irene V. Allen (Associate), New Brunswick, Can.—1 reprint.
  - Joseph L. Hollander (Associate), Hot Springs National Park, Ark.—1 reprint.
  - Victor H. Kugel (Associate), Cambridge, Ohio—2 reprints.
  - B. Oliver Lewis, F.A.C.P., Galveston, Tex.—2 reprints.
  - George X. Schwemlein (Associate), Chicago, Ill.—2 reprints.
  - Norman R. Shulack (Associate), Brooklyn, N. Y.—2 reprints.
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The Council Committee on Public Health and Education of the Medical Society of the State of New York is sponsoring courses of instruction in Pulmonary Diseases and Tuberculosis under the auspices of the New York State Department of Health. These courses will be given at Hermann M. Biggs Memorial Hospital, Ithaca, N. Y., Homer Folks Tuberculosis Hospital, Oneonta, N. Y., Mount Morris Tuberculosis Hospital, Mount Morris, N. Y., New York State Hospital, Ray Brook, N. Y., and are designed primarily for medical officers returning from service with the Armed Forces. Each State Tuberculosis Hospital has arranged to accommodate four residents for a minimum period of instruction of three months or a maximum of twelve months. This training will provide a basic background for a career in sanatorium work, public health, or later specialization in thoracic diseases. The plan is endorsed by the medical



schools in Albany, Buffalo, Rochester, and Syracuse, as well as by the United States Public Health Service which has allocated funds to provide a reasonable monthly stipend, if certain qualifications can be met by applicants. Inquiries should be addressed to Robert E. Plunkett, M.D., General Superintendent of Tuberculosis Hospitals, New York State Department of Health, Alfred E. Smith State Office Building, Albany 1, New York.

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The next written examination of the American Board of Internal Medicine will be held on October 21. The closing date for the acceptance of applications is July 1. There are no written examinations in the sub-specialties:

Allergy  
Cardiovascular Disease  
Gastro-enterology  
Tuberculosis

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The School of Medicine of the College of Medical Evangelists, Los Angeles, California, has developed its graduate teaching program along four lines:

Residency  
Fellowship  
Precepteeship  
Graduate Courses

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Preparation for Specialty Board examination is stressed. Further information may be obtained from the Dean, W. F. Norwood, M.D., Los Angeles Division, College of Medical Evangelists, White Memorial Hospital, Boyle & Michigan Avenues, Los Angeles 35, California.

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Northwestern University, Evanston, Ill., plans to develop its Chicago campus to meet the vastly increased need for research in medicine, dentistry, law, business, government, and aeronautics. The new program will require from \$95,000,000 to \$150,000,000 to erect in Chicago 16 new buildings, and provide a large endowment for research and teaching. It is estimated that from 20 to 25 years will be required to put this plan in complete operation.

Among the various objectives included in this campus plan of Northwestern University, top listing has been given to the development of a great medical center that will place major emphasis on medical research. Ten new buildings are envisaged which, together with the necessary equipment and endowment will require a sum ranging from \$63,000,000 to \$95,000,000. It is believed that this proposed development, in time, will make Chicago the world's greatest center for medical teaching and research, according to Dr. James Roscoe Miller, F.A.C.P., Dean of Northwestern's Medical School.

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The faculty of Columbia University College of Physicians and Surgeons has established residencies and fellowships to provide training in physical medicine on a graduate level. Applications should be submitted to the directors of the following hospitals:

Presbyterian Hospital, 620 West 168th Street, New York 32.  
New York Post-Graduate Medical School and Hospital, 303 East 20th Street,  
New York 3.

Mount Sinai Hospital, Fifth Avenue at 100th Street, New York 29.  
 St. Luke's Hospital, 421 West 113th Street, New York 25.  
 Goldwater Memorial Hospital, Welfare Island, New York.  
 Montefiore Hospital, 150 East Gunhill Road, New York 67.  
 Hospital for Joint Diseases, 1919 Madison Avenue, New York 35.

The Michigan State Medical Society and the medical schools of the University of Michigan, Ann Arbor, and Wayne University, Detroit, are coöperating in a course on medical economics. Details of the course may be obtained from the Dean's office at each university.

The Norton Medical Award of \$3500 which is offered by W. W. Norton & Company, Inc. of 70 Fifth Avenue, New York 11, N. Y., to encourage the writing of books on medicine and the medical profession for the layman, is now open for competition. Terms of the Award and publication may be obtained from the Publishers. The Award is offered for a book to be published in 1947. Announcement will be made shortly of the winning book for 1946. Closing date for submission of manuscripts this current year is November 1.

Examinations for appointments of medical officers in the Regular Corps of the United States Public Health Service are now under way at various convenient localities throughout the country. Examinations will be oral and written. The written examination will be held on May 14, 15 and 16 at places convenient to the candidate and the Service. The oral examination will begin at 9:00 a.m. at the places and dates listed below:

Atlanta, Georgia—Malaria Control in War Areas, 605 Volunteer Bldg. . .	Apr. 22
Baltimore, Maryland—Marine Hospital, Wyman Park Drive & 31st Street	May 9
Boston, Massachusetts—Marine Hospital, 77 Warren Street (Brighton)	May 6
Chicago, Illinois—Marine Hospital, 4141 Clarendon Avenue . . . . .	Apr. 30
	May 1
Cleveland, Ohio—Marine Hospital, Fairhill Road & E. 124th Street . . .	May 3
Denver, Colorado—617 Colorado Bldg. . . . .	Apr. 8
Detroit, Michigan—Marine Hospital, Windmill Pointe . . . . .	May 2
Fort Worth, Texas—U. S. Public Health Service Hospital . . . . .	Apr. 25
Kirkwood, Missouri—near St. Louis—Marine Hospital, 525 Couch Ave. .	Apr. 26, 27
Los Angeles, California—USPHS Relief Station, 406 Federal Building .	Apr. 9
Minneapolis, Minn.—Office of Indian Affairs, 218 Federal Office Bldg. .	Apr. 29
New Orleans, Louisiana—Marine Hospital, 210 State Street . . . . .	Apr. 23, 24
New York, New York—Marine Hospital, Stapleton, Staten Island . . . .	May 7, 8
Norfolk, Virginia—Marine Hospital, Hampton Blvd., Larchmont . . . .	May 10
San Francisco, California—Marine Hospital, 14th Ave. & Park Blvd. . .	Apr. 10, 11
Seattle, Washington—Marine Hospital, Judkins St. & 14th Ave. South .	Apr. 12, 13
Washington, D. C.—USPHS Dispensary, Fourth and D Streets SW. . .	Apr. 4
	May 13

Application forms may be obtained by writing to the Surgeon General, U. S. Public Health Service, Washington 25, D. C.

The University of Rochester School of Medicine and Dentistry is sponsoring two programs for the benefit of returning veteran medical officers. The first is a Residency-Fellowship Program designed to qualify veteran physicians as specialists. This has been made possible by the creation of additional positions in the usual clinical fields and by increase in the number of Fellowships in the basic medical sciences.

To meet the needs of returning medical officers who desire a general review of the whole field of medicine, a Postgraduate Refresher Course has been established, which will run for a period of six weeks and cover the entire field of medicine and surgery and the specialties in a general way. Registration will be limited to a maximum of 30 men, and the course may be repeated if there is sufficient demand. Letters of application should be addressed to the Dean's Office, School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, New York.

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A National Society for Medical Research is being organized to protect animal experimentation in biology, dentistry, pharmacy and veterinary medicine from the inroads of political interference. Plans for this new society were sponsored by the Council on Medical Education and Hospitals of the American Medical Association and the Federation of State Medical Boards. The functions of the National Society for Medical Research shall be:

1. Education of the public relative to the necessity, importance, humane character and accomplishments of animal experimentation in medicine and biology.
2. Aid in preventing the enactment of national and local legislation restrictive to animal experimentation.
3. Promotion of legislation providing for the protection of animal experimentation in medicine and biology.

Under the auspices of the Association of American Medical Colleges an organizing board of directors has been selected. Dr. A. J. Carlson, F.A.C.P. (University of Chicago) Chairman, Dr. Andrew C. Ivy, F.A.C.P. (Northwestern University) Secretary and Dr. C. Sidney Burwell, F.A.C.P. (Harvard Medical School) Chairman of the Executive Committee.

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Professional and physical examinations for the Medical Corps, U. S. Navy, will be conducted at various naval hospitals from May 6-10. Successful candidates will be appointed as Assistant Surgeon and Acting Assistant Surgeon with the rank of Lieutenant (junior grade). Application forms and other data may be obtained by writing to the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to March 13, 1946 inclusive):

F. Dennette Adams, Boston, Mass. (Col., MC, AUS)  
Ruel L. Alden, Hempstead, N. Y. (Major, MC, AUS)  
Edward L. Alexander, Newport News, Va. (Comdr., MC, USNR)

Crawford N. Baganz, Lyons, N. J. (Lt. Comdr., MC, USNR)  
John L. Baube, Mt. Vernon, Ohio (Major, MC, AUS)  
James R. Bell, Cleveland, Ohio (Lt. Col., MC, AUS)

William O. Benenson, Napanoch, N. Y. (Lt. Col., MC, AUS)  
Z. Taylor Bercovitz, New York, N. Y. (Lt. Col., MC, AUS)  
Earl J. Bieri, Hot Springs, Ark. (Capt., MC, AUS)  
Louis F. Bishop, Jr., New York, N. Y. (Lt. Col., MC, AUS)  
Everett O. Black, Fredonia, N. Y. (Major, MC, AUS)  
Morris Block, New York, N. Y. (Comdr., MC, USNR)  
Allen G. Brailey, Brookline, Mass. (Lt. Comdr., MC, USNR)  
Ward W. Briggs, Baltimore, Md. (Comdr., MC, USNR)  
Leon Bromberg, St. Louis, Mo. (Capt., MC, USNR)  
Frederick S. Bruckman, San Francisco, Calif. (Major, MC, AUS)  
Burdette J. Buck, Hartford, Conn. (Lt. Col., MC, AUS)  
Aaron L. Burger, Brooklyn, N. Y. (Lt. Col., MC, AUS)  
George G. Burkley, Pittsburgh, Pa. (Lt. Comdr., MC, USNR)  
William C. Buschemeyer, Louisville, Ky. (Capt., MC, AUS)

Mortimer J. Cantor, Brooklyn, N. Y. (Major, MC, AUS)  
A. Albert Carabelli, Trenton, N. J. (Lt. Col., MC, AUS)  
H. Dumont Clark, Denver, Colo. (Lt. Col., MC, AUS)  
Howard C. Coggeshall, Dallas, Tex. (Major, MC, AUS)  
William E. Costolow, Los Angeles, Calif. (Capt., MC, USNR)  
P. Thurman Crawford, Memphis, Tenn. (Lt. Comdr., MC, USNR)  
Hatch W. Cummings, Jr., Houston, Tex. (Comdr., MC, USNR)

John S. Davis, Jr., New York, N. Y. (Lt. Col., MC, AUS)  
E. Rankin Denny, Tulsa, Okla. (Col., MC, AUS)  
Mark S. Dougherty, Jr., Atlanta, Ga. (Lt. Comdr., MC, USNR)  
Eugene H. Drake, Portland, Maine (Capt., MC, USNR)  
Edgar Durbin, Denver, Colo. (Lt. Col., MC, AUS)

Frederick A. Eigenbrod, New Orleans, La. (Major, MC, AUS)  
Earl B. Erskine, Jamaica, L. I., N. Y. (Comdr., MC, USN)  
Peter Everett, III, New Orleans, La. (Capt., MC, AUS)  
Harold K. Eynon, Collingswood, N. J. (Lt. Col., MC, AUS)

John L. Ferry, Akron, Ind. (Major, MC, AUS)  
David Fertig, Hartsdale, N. Y. (Lt., MC, USNR)  
Luther I. Fisher, Bethlehem, Pa. (Comdr., MC, USNR)  
Ralph L. Fitts, Grand Rapids, Mich. (Capt., MC, AUS)  
Hiland L. Flowers, New York, N. Y. (Lt. Col., MC, AUS)  
Thomas F. Frist, Nashville, Tenn. (Major, MC, AUS)

Daniel M. Green, Jacksonville, Fla. (Lt. Col., MC, AUS)  
Edward B. Grossman, New York, N. Y. (Major, MC, AUS)

Frederic W. Hall, Winfield, Kan. (Capt., MC, AUS)  
Reid R. Heffner, New Rochelle, N. Y. (Major, MC, AUS)  
Francis J. Heringhaus, Mansfield, Ohio, (Lt. Col., MC, AUS)  
Iredell M. Hinnant, Cleveland, Ohio (Lt. Col., MC, AUS)  
Samuel J. Hoffman, Chicago, Ill. (Lt. Col., MC, AUS)  
Lyman H. Hoyt, Boston, Mass. (Comdr., MC, USNR)  
Hyman M. Hurevitz, Davenport, Iowa (Major, MC, AUS)

Cullen W. Irish, Los Angeles, Calif. (Lt. Col., MC, AUS)

William A. Jeffers, Philadelphia, Pa. (Major, MC, AUS)  
Hartwell Joiner, Gainesville, Ga. (Major, MC, AUS)  
Benjamin Juliar, Detroit, Mich. (Capt., MC, AUS)

Boyd G. King, Cleveland, Ohio (Lt. Col., MC, AUS)  
Robert C. Kirk, Columbus, Ohio (Major, MC, AUS)  
Gerald Klatskin, New Haven, Conn. (Major, MC, AUS)  
Phillip T. Knies, Columbus, Ohio (Col., MC, AUS)  
Israel Kopp, Roxbury, Mass. (Capt., MC, AUS)  
Philip Krainin, New York, N. Y. (Lt. Comdr., MC, USNR)

John J. Maisel, Buffalo, N. Y. (Major, MC, AUS)  
Tim J. Manson, Chattanooga, Tenn. (Capt., MC, AUS)  
Walter B. Martin, Norfolk, Va. (Col., MC, AUS)  
Jesse McCall, Newton, N. J. (Lt. Col., MC, AUS)  
Robert P. McCombs, Philadelphia, Pa. (Lt., MC, USNR)  
Francis E. McDonough, Boston, Mass. (Lt. Col., MC, AUS)  
Currier McEwen, New York, N. Y. (Lt. Col., MC, AUS)  
John B. McKee, Winchester, Va. (Lt. Col., MC, AUS)  
Theodore H. Mendell, Philadelphia, Pa. (Lt. Col., MC, AUS)  
Joseph Mignone, New Haven, Conn. (Lt., MC, USNR)  
Samuel Millman, Brooklyn, N. Y. (Lt. Col., MC, AUS)  
Charles S. Mills, Phoenix, Ariz. (Major, MC, AUS)  
Robert G. Murphy, Providence, R. I. (Capt., MC, AUS)

Robert J. Needles, St. Petersburg, Fla. (Lt. Col., MC, AUS)  
Arthur D. Nichol, Cleveland, Ohio (Lt. Col., MC, AUS)  
John Noll, Jr., Youngstown, Ohio (Lt. Col., MC, AUS)

Maurice C. Pincoffs, Baltimore, Md. (Col., MC, AUS)  
Ross J. Porritt, Pontiac, Mich. (Major, MC, AUS)  
John M. Porter, Concordia, Kan. (Comdr., MC, USNR)  
Robert T. Porter, Greeley, Colo. (Major, MC, AUS)

Richard Z. Query, Jr., Charlotte, N. C. (Major, MC, AUS)

William O. Ramey, Cincinnati, Ohio (Capt., MC, USNR)  
Jack O. W. Rash, Miami, Fla. (Major, MC, AUS)  
Joseph W. Rastetter, Milwaukee, Wis. (Comdr., MC, USNR)  
E. Burkett Reed, Lincoln, Nebr. (Capt., MC, AUS)  
William D. Reid, Kezar Falls, Maine (Lt. Comdr., MC, USNR)  
Anthony E. Reymont, Santa Fe, N. M. (Capt., MC, USNR)  
Edwin L. Rippy, Dallas, Tex. (Lt. Col., MC, AUS)  
Abraham I. Rosenstein, New York, N. Y. (Capt., MC, AUS)  
Henry C. Rosenstiel, Freeport, Ill. (Major, MC, AUS)  
Thomas L. Ross, Jr., Macon, Ga. (Major, MC, AUS)  
Maurice J. Rotkow, Des Moines, Iowa (Capt., MC, AUS)  
Chauncey L. Royster, Raleigh, N. C. (Major, MC, AUS)  
J. Griswold Ruth, Benton Harbor, Mich. (Capt., MC, AUS)

S. Marion Salley, Miami, Fla. (Lt. Col., MC, AUS)  
John B. Schwedel, New York, N. Y. (Comdr., MC, USNR)

Euclid M. Smith, Hot Springs, Ark. (Lt. Col., MC, AUS)  
 Raymond A. Sokolov, Detroit, Mich. (P. A. Surgeon, USPHS (R))  
 Robert F. Solley, New York, N. Y. (Comdr., MC, USNR)  
 Irving E. Steck, Chicago, Ill. (Major, MC, AUS)  
 Charles W. Steele, Lewiston, Maine (Lt. Col., MC, AUS)  
 Stuart Dos Passos Sunday, Baltimore, Md. (Lt. Col., MC, AUS)

Myer Teitelbaum, Detroit, Mich. (Capt., MC, AUS)  
 Kent H. Thayer, Phoenix, Ariz. (Major, MC, AUS)  
 Charles E. Thompson, Omaha, Nebr. (Major, MC, AUS)  
 Kilby P. Turrentine, Kinston, N. C. (Lt. Comdr., MC, USNR)

Lee D. van Antwerp, Meriden, Conn. (Major, MC, AUS)  
 Raymond G. Vinal, Norwell, Mass. (Major, MC, AUS)

Levi M. Walker, Atlantic City, N. J. (Major, MC, AUS)  
 Harry A. Warren, Champaign, Ill. (Lt. Col., MC, AUS)  
 Oliver W. Welch, Fairfield, Ala. (Capt., MC, AUS)  
 Martin H. Wendkos, Philadelphia, Pa. (Major, MC, AUS)  
 William G. Weston, Arkansas City, Kan. (Major, MC, AUS)  
 Clarence B. Whims, Ventnor City, N. J. (Major, MC, AUS)  
 Asher A. White, Minneapolis, Minn. (Major, MC, AUS)  
 Duncan Whitehead, Utica, N. Y. (Lt. Col., MC, AUS)  
 Arthur T. Wyatt, Lillington, N. C. (Lt. Col., MC, AUS)

Richard H. Young, Evanston, Ill. (Lt. Col., MC, AUS)

#### 1945 OPERATIONS

#### THE AMERICAN COLLEGE OF PHYSICIANS

The accounts of the American College of Physicians, ending December 31, 1945, have been audited by a Public Accountant, and the following statements are printed for the information of members. The net increase in the Endowment Fund was \$26,453.45 and in the General Fund, \$16,592.56, increasing these Funds to \$196,196.84 \$225,278.44, respectively; total assets of the College, December 31, 1945, \$421,475.28.

#### BALANCE SHEET

##### *General Fund*

##### *Current Assets:*

Cash in Bank and on Hand .....	\$ 51,072.73	
Accounts Receivable .....	5,738.81	
Loans Receivable .....	1,500.00	
Inventory of Keys, Pledges & Frames .....	364.05	
Accrued Income, General Fund Investments \$ 528.55		
Accrued Income, Endowment Fund		
investments .....	1,202.48	1,731.03
Investments, at Book Value .....	\$126,454.79	
Insurance Deposit .....	555.00	\$187,416.41

*Fixed Assets:-*

College Headquarters, Real Estate .....	\$57,728.45		
Less: Reserve for Depreciation .....	9,000.00	48,728.45	
Investment, Real Estate, 404-12 S. 42nd St. ....		9,170.50	
Furniture & Equipment .....	12,322.98		
Less: Depreciation .....	9,525.07	2,797.91	60,696.86
Gross Assets, General Fund .....			\$248,113.27

*Liabilities:**Current:*

Accounts Payable .....	\$ 1,170.32		
Chicago Postgraduate Fund .....	713.30	1,883.62	

*Deferred Income:*

Subscriptions to the "Annals of Internal Medicine," paid in advance .....	17,974.47		
Advertising in "Annals of Internal Medicine," paid in advance .....	692.44	18,666.91	

*Reserve:*

Philadelphia Postgraduate Fund .....		2,284.30	
Total Liabilities .....	\$ 22,834.83		
General Fund .....	225,278.44	\$248,113.27	

## SUMMARY OF OPERATIONS, General Fund

*Year Ending December 31, 1945**Income:*

Annual Dues .....		23,684.67	
Initiation Fees .....		9,815.00	
Subscriptions, "Annals of Internal Medicine" .....		42,723.96	
Advertising, "Annals of Internal Medicine" .....		14,706.98	
Income from Investments, General Fund .....		5,564.80	
Income from Investments, Endowment Fund .....		5,795.64	
Dividends on Perpetual Insurance Deposit .....		60.00	
Keys, Pledges and Frames .....		17.54	
1943 Membership Roster .....		1.50	
Rent, 404-12 S. 42nd St. ....	\$ 1,620.00		
Less: Maintenance .....	\$322.87		
Water Tax .....	14.96		
Real Estate Taxes .....	489.55	827.38	792.62
Profit from Sale of Securities (General Fund) .....		1,684.64	

TOTAL ..... \$104,847.35

*Expenditures:*

Salaries .....	28,513.23	
Postage, Telephone and Telegraph .....	3,983.27	
Office Supplies and Stationery .....	1,489.78	
Printing .....	25,876.82	
Traveling Expenses .....	2,939.55	
Miscellaneous Expenses .....	1,667.07	

## College Headquarters:

Maintenance .....	\$ 2,037.99	
Heat, Light, Gas & Water .....	780.05	
Taxes .....	170.77	
Insurance .....	72.22	3,061.03

Depreciation on Building .....	\$ 1,000.00	
Depreciation on Furniture & Equipment .....	833.99	1,833.99

Investment Counsel & Custodian Fees .....	527.53	
Regional Meetings .....	1,566.43	
Postgraduate Courses, 1945 .....	1,939.68	
War-Time Graduate Medical Meetings .....	5,000.00	
Collection & Exchange .....	26.53	
Loss on Sale or Maturity of Investments, General Fund .....	159.62	
1945 Membership Roster .....	188.28	
1945 Annual Meeting .....	15.08	
Pension Fund .....	3,481.90	82,269.79

Net Income Year 1945 ..... \$ 22,577.56

*General Fund*

Balance, January 1, 1945 .....	208,685.88	
Less: Transfer to Endowment Fund of Initiation		
Fees of Life Members .....	5,985.00	202,700.88
		<u>\$225,278.44</u>

## BALANCE SHEET

*Endowment Fund**Current Assets:*

Cash in Bank .....	\$ 22,163.61	
Accrued Income .....	1,202.48	
Investments .....	174,033.23	\$197,399.32
Endowment Fund Principal .....	196,196.84	
Accrued Income Due General Fund .....	1,202.48	\$197,399.32



*Endowment Fund Operation.*

Endowment Fund Principal, January 1, 1945 ..... \$169,743.39

Add:

Life Membership Fees Received during 1945 ..... \$ 17,500.00

Transfer of Initiation Fees of Life Members from

General Fund ..... 5,985.00

Net Gain from Sale of Endowment Fund

Investments ..... 2,968.45      26,453.45

Endowment Fund ..... \$196,196.84

## OBITUARIES

## DR. FRANK HERBERT BARTLETT, JR.

Dr. Frank Herbert Bartlett, Jr. F.A.C.P., was born in Lynn, Mass., July 25, 1894. After receiving his early education in the Lynn English High School, he entered Tufts Medical College from which he was graduated in 1919. Soon after graduation, he was appointed Assistant Director of the Central Maine Sanitarium in Westfield, Maine. From there he went to Healthwinn, the St. Joseph County Tuberculosis Sanitarium, South Bend, Indiana. In 1923, he became Director of the Livingstone County Tuberculosis Hospital at Pontiac, Illinois. On December 6, 1926, he became Director of the Muskegon County Tuberculosis Sanitarium, Muskegon, Michigan, and continued in that capacity until his death.

He was a Trustee of the Michigan Tuberculosis Society, a member of the American Trudeau Society, a Fellow of the American College of Physicians, a member of the Mississippi Valley Conference on Tuberculosis, and the National Tuberculosis Association. He was a past president of the Muskegon County Medical Society, a thirty-second degree Mason and a member of the B. P. O. Elks, Rotary Club, and the Alpha Kappa Kappa Medical Fraternity.

Dr. Bartlett was deeply interested in his specialty and during his time as Director of the Muskegon County Tuberculosis Sanitarium, the death rate from tuberculosis in Muskegon County decreased 74 per cent.

He died January 25, 1946, from a fractured skull, resulting from a fall down the basement stairs at his home.

WILLIAM M. LEFEVRE, M.D., F.A.C.P.

## DR. GEORGE EMANUEL HOLTZAPPLE

George Emanuel Holtzapple, M.D., Sc.D. (Hon.), F.A.C.P., York, Pennsylvania, died at his home on Washington's Birthday, February 22, at the age of eighty-three years and nine months. He was born in West Manchester Township, York County, May 22, 1862, where he attended the public school for a grand total of fifty-five months—most of his early education having been obtained at his country home by the flicker of a candlestick. He later attended the York Collegiate Institute and York County Academy, walking four and a half miles morning and evening, and living on a lunch that cost three to five cents! He began his study of medicine at the Baltimore Medical College, later transferring to Bellevue Medical College, New York, where he was graduated in 1884. He later did postgraduate work at the New York Postgraduate Medical School, Johns Hopkins Medical School, and in various clinics throughout the country. Dr. Holtzapple was ever interested in keeping in close touch with the latest developments in medi-

cine, and attended the Annual Sessions of the College with great regularity. He also took some of its postgraduate courses up until the age of eighty.

Dr. Holtzapple was attending physician, and later consulting physician and chief of the Neuropsychiatric Clinic, York Hospital, and for a period of five years was President of the Staff. He was a Member, and Past President of the York County Medical Society; Member, Medical Society of the State of Pennsylvania (one-time Chairman of the Medical Section); American Medical Association; American College of Physicians (1920). He was also a Diplomat of the American Board of Internal Medicine (1937).

Among his outstanding achievements were his pioneer work in the administration of oxygen for the relief of anoxemia in pneumonia, and his brilliant observations in a large group of Family Periodic Paralysis.

Dr. Holtzapple was also deeply interested in civic and religious affairs in his community and held many posts of honor and trust in its various important activities, being at one time President of the School Board of York.

He was a fine and cultured gentleman, of high moral character, and a distinguished clinician. His professional attainments were of the very highest order, and he was truly a profound student, and a clinician of excellent judgment. His loss will be very keenly felt by the medical profession and the community he served so well and long.

Dr. Holtzapple is survived by his widow and three children.

JULIUS H. COMROE, M.D., F.A.C.P.

### DR. NEWTON GURDON EVANS

Dr. Newton Gurdon Evans, B.S., F.A.C.P., of South Pasadena, died December 19, 1945 at the White Memorial Hospital, Los Angeles, of carcinoma, at the age of seventy-one.

Dr. Evans was born at Hamilton, Missouri, June 1, 1874. He attended Battle Creek College, later transferring to Union College, from which he received his B.S. degree in 1895. He then entered the American Medical Missionary College, later transferring to Cornell University Medical College, receiving his M.D. degree in 1900. He studied post graduate at the University of Chicago, Cornell University and the Mayo Foundation. During 1900-1905 he was Instructor in Histology, American Medical Missionary College; Professor of Pathology, 1908-1911, University of Tennessee College of Medicine; Professor of Pathology, Vice President of the faculty, later becoming President, College of Medical Evangelists, Los Angeles. He was Chairman of the Board of the Alumni Research Foundation, College of Medical Evangelists; Pathologist and Secretary of the Malignancy Board, Los Angeles County Hospital; Lieutenant Colonel (inactive) of the Medical Reserve Corps, U. S. Army. He was former President of the Los Angeles Pathological Society, Los Angeles Cancer Society, American Association of

Pathologists and Bacteriologists; member of the American Society of Clinical Pathologists, Los Angeles Academy of Medicine, California State Medical Association and American Association for the Advancement of Science. He was a Fellow of the American Medical Association, and The American College of Physicians, the latter since 1921, and a Counselor of the Surgeon General's Library.

In early 1945 his portrait was presented to the White Memorial Library.

ROY E. THOMAS, M.D., F.A.C.P.,  
Governor for Southern California

#### DR. CHARLES T. WAY

Dr. Charles T. Way, F.A.C.P., was born near Taylor, North Dakota, in 1887. He attended Beloit College, Wisconsin, graduating with a B.S. degree in 1914. After three years of teaching, he turned to medicine and attended Western Reserve University School of Medicine graduating in 1921. Following an internship and residency at Saint Luke's Hospital, Cleveland, Ohio, he began the practice of medicine and was closely associated with Saint Luke's Hospital until ill health forced his resignation from the position of Director of Medicine. Dr. Way was an enthusiastic and able teacher. He held the positions, successively, of Instructor, Senior Instructor, and Assistant Clinical Professor of Medicine at his Alma Mater. He was always interested in organized medicine and took an active part in the Cleveland Academy of Medicine, serving for a number of years on its Board of Directors and was its President from 1940-1941. His industry, open, friendly personality, and ability not only brought him recognition in his profession but a host of devoted friends. He was an ardent hunter and lover of the out-of-doors, and an enthusiastic member of the Canadian Camp Fire Club. He died on February 4, 1946, from arteriolar nephrosclerosis and uremia, a disease to which he had devoted a considerable portion of his research capacity and to the knowledge of which he had made numerous scientific contributions.

JOSEPH M. HAYMAN, JR., M.D., F.A.C.P.

#### DR. ARCHIBALD D. SMITH

Archibald D. Smith, M.D., F.A.C.P., Garden City, New York, died at the Brooklyn Hospital, November 22, 1945, of coronary thrombosis. Dr. Smith was born in 1876, received his A.B. degree in 1898 from Yale University and his M.D. degree in 1902 from Columbia University College of Physicians and Surgeons. For many years he was Pediatrician at the

Brooklyn Hospital, and thereafter Consulting Pediatrician at that institution and at the Rockaway Beach Hospital and Dispensary.

Dr. Smith was a former president of the Brooklyn Academy of Pediatrics and the Brooklyn Pediatric Society; a member of the American Academy of Pediatrics. He had been head of a civilian defense medical unit in Garden City during World War II.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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NUMBER 5

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## A CLINICAL ANALYSIS OF PRIMARY ATYPICAL PNEUMONIA WITH A DISCUSSION OF ELEC- TROCARDIOGRAPHIC FINDINGS \*

By JOSEPH F. PAINTON, Lt. Colonel, F.A.C.P., ALFRED M. HICKS, Major,  
and SAMUEL HANTMAN, Major, M.C., A.U.S.

DURING the last few years, numerous reports have appeared in medical literature describing a type of pneumonia differing from both lobar and bronchopneumonia. Many confusing terms and designations have been suggested for this disease but it is generally referred to as atypical pneumonia.

Although the disease is commonly regarded as a new entity, Dingle and Finland,<sup>1</sup> in reviewing the literature on this type of pneumonia, found that as long ago as 1872, a similar disease and pathological picture was described. They noted also the existence of a condition in the military forces, even before the pandemic of influenza in 1918, called by such names as "soldier's pneumonia" and "catarrhal fever." It seems apparent even from this meager information that the disease entity is probably not new at all, but merely has escaped recognition because of the inability of physicians fully to utilize the roentgen-ray in their study of obscure respiratory infection.

Efforts to determine a common causative agent of this disease process have not met with much success. Isolated cases and even small groups of cases have been shown to be caused by various filterable viruses, such as influenza A and B, psittacosis, ornithosis and the virus of lymphocytic choriomeningitis. Atypical pneumonic lesions have been observed in several of the rickettsial diseases, namely, typhus, Rocky Mountain spotted fever and both the Australian and American Q fever.<sup>2</sup> The clinical picture of pulmonary coccidioidomycosis, a fungus disease, not infrequently resembles that of atypical pneumonia. The protozoan, toxoplasma<sup>3</sup> has been reported to produce an atypical pneumonic process. Finland<sup>4</sup> has stated that the pneumococcus and even the streptococcus may produce atypical pulmonary processes, particularly in children.

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\* Received for publication July 14, 1945.

In all probability, this disease is not a single entity, but a syndrome produced by a variety of agents, both non-bacterial and bacterial.

Even after all attempts to determine an etiologic agent have been exhausted, there still is an appreciable number of cases in which the clinical and roentgenographic picture is that of atypical pneumonia. This condition, which has been rather prominent in military installations<sup>5, 6, 7, 8, 9, 10</sup> has been designated by the Surgeon General as primary atypical pneumonia, etiology unknown.

It is with the latter group that this paper is concerned. During the period from May, 1943 to April, 1944, 678 cases were admitted to the Regional Station Hospital, Greensboro, North Carolina, with the diagnosis of pneumonia. Of this number, 187 were considered to be lobar pneumonia of pneumococcic origin. The remainder, or 491, were classified as atypical in character.

This present analysis is based on the clinical experience with 321 of these cases, in which the etiology was unknown or undetermined. Inasmuch as laboratory facilities were not available for extensive virus studies, it is possible that some cases may have been due to such an agent, but with the evidence at hand they had to be regarded as of unknown etiology. The question might arise as to whether some of these cases were not of bacterial origin, as has been suggested by Finland.<sup>4</sup> Any answer to that problem is difficult, but sputum studies and blood cultures failed to corroborate this possibility. The latter will be discussed in detail later.

The establishment of absolute diagnostic criteria in this disease is impossible. However, the following points were considered before the case was designated as one of primary atypical pneumonia:

1. Inability to determine a known etiological agent.
2. History of gradual onset.
3. Benign but prolonged course.
4. Minimal physical findings.
5. Roentgenographic evidence of mottled infiltration usually lacking the marked homogeneous density of lobar pneumonia.
6. An essentially normal initial leukocyte count.
7. In general, poor response to sulfonamide therapy.

Obviously, strict adherence to all of these criteria was not feasible, so that each case was considered individually. In some of the cases, the diagnosis had to be made by exclusion.

*Age, Sex, and Race Distribution.* Chart 1 illustrates the relative frequency of the various age groups. In this series those aged 18 predominated, approximately 30 per cent falling into this group. Eighty per cent of the cases occurred between the ages of 18 and 26, which would be expected in a post where Air Corps personnel were undergoing training. The frequent occurrence of this disease in young adults is confirmed by recent reports in the literature.<sup>1, 2, 4, 5, 6, 7, 8, 9, 11</sup> All of these investigations were made in either

military posts or civilian schools, so that the age incidence would of necessity be limited to the younger age groups. However, it is notable that relatively little has been published concerning atypical pneumonia in the older age groups.

Inasmuch as only one case in this series was a female, no data on sex incidence are included.

In this series, 294 of the cases were white and 27 were colored. Although it was difficult to interpret these figures, owing to the varying

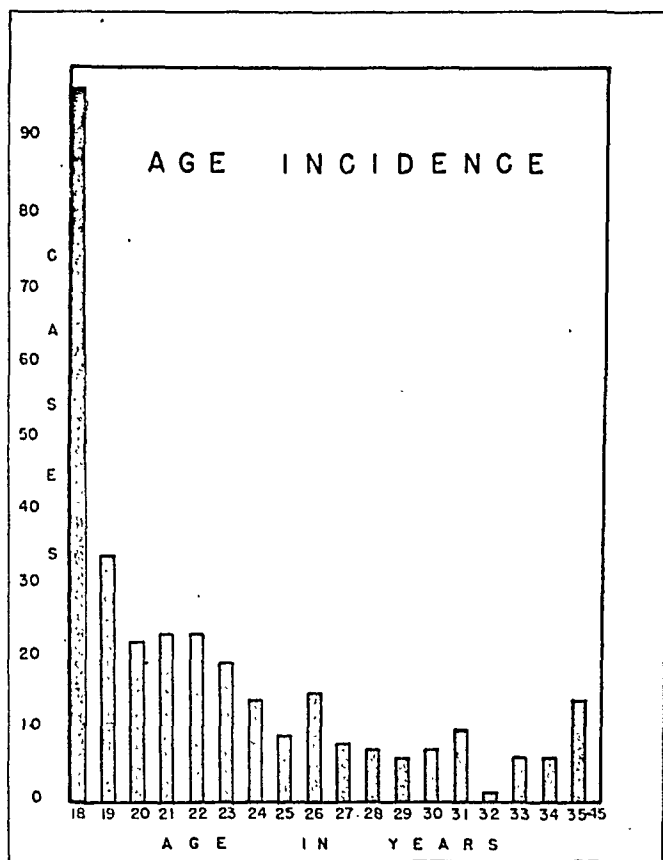


CHART 1.

monthly strengths of white and colored troops, it was our impression that the disease was not quite so prevalent in the colored as in the white race.

It was also thought that atypical pneumonia was more frequent in recruits than in soldiers who had finished their training; Chart 2 demonstrates the incidence of the disease according to the length of service. The highest incidence, 76.6 per cent, occurred during the first three months of service. This condition would be anticipated in a basic training center, where the majority of the personnel were trainees who remained at the post for only a short interval. Eighty-five and three-tenths per cent of the cases developed during the first six months of service, which suggests that this disease, at



least in some respects, resembles other "contagious" diseases which show a similarly high incidence during this period. In other words, the longer the soldier was in service, the less prone he was to develop atypical pneumonia. Of the 321 cases, only 16 had been in service in excess of one year. This group would be generally classified as permanent party personnel, who constituted about one-seventh of the entire post strength. On the basis of incidence for the entire post, this number should have been four times as many as actually occurred. In the main, the disease appeared most frequently in soldiers who had little military service. Similar observations relevant to the high incidence in recent inductees have been reported from other military installations.<sup>6</sup>

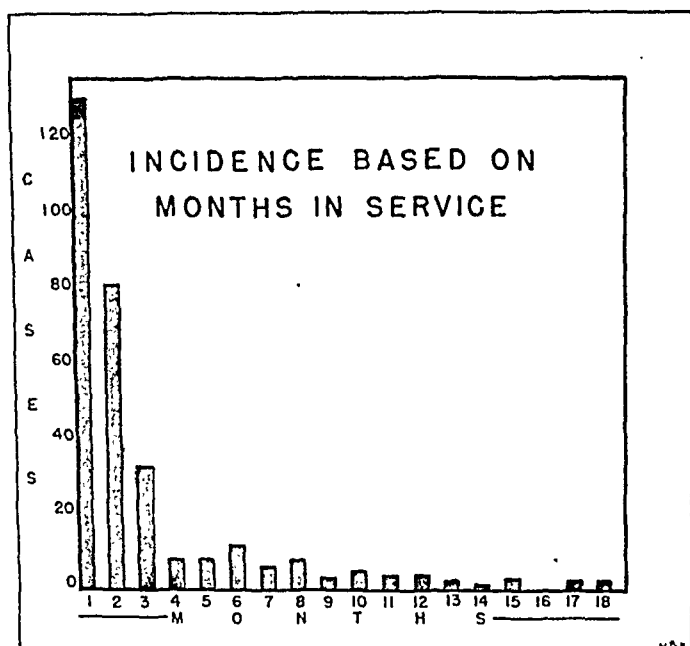


CHART 2,

*Seasonal Incidence.* Chart 3 portrays the seasonal incidence in months for both atypical and lobar pneumonia, contrasted with the post strength. If the number of cases per thousand troops is used as a basis, it is evident that March stands out as the month of greatest incidence for atypical pneumonia. The next in frequency were December, January, and February. Lobar pneumonia, on the other hand, attained its highest incidence in January and was less commonly observed during the month of March. A situation which prevailed in this portion of North Carolina does not necessarily represent the incidence that would be expected throughout the country as a whole. It is also apparent that primary atypical pneumonia occurred quite commonly throughout the entire year, whereas lobar pneumonia, though appearing sporadically in the summer months, was essentially a late fall and winter disease in this locality.

*Origin of Cases by States.* In an effort to determine whether soldiers transported from one state to another far removed from their native environment were more susceptible to this disease than if they remained in relative propinquity to their homes, a survey was made to determine the soldier's home state. It was found that most soldiers originally came from New York, Pennsylvania, Massachusetts, New Jersey, North Carolina, Connecticut and Georgia, in the order named. It was, therefore, our impression that although changes from one climate to another may be a factor

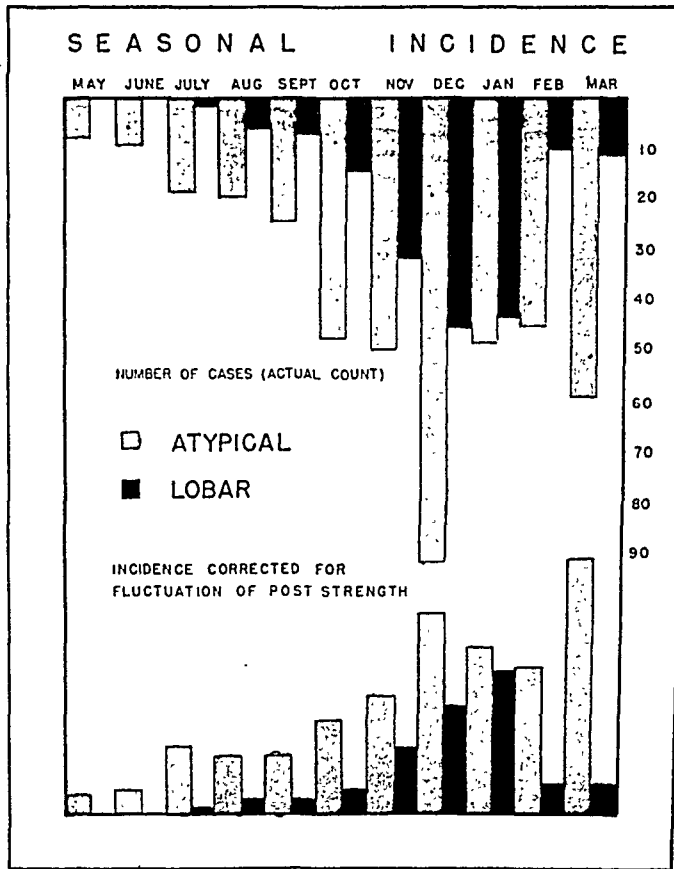


CHART 3.

in this disease, no statistical data were available as to the states which contributed the highest percentages to our training personnel. It is probable that the states which predominated in this series were those which contributed the greatest proportion of trainees to this post. In connection with this survey, it seemed expedient to ascertain whether the soldier had resided in a city or lived in a less congested area. In this series of 321 cases, 259, or 80 per cent, formerly resided in urban communities, whereas 62, or 20 per cent, were inhabitants of rural districts. It was our impression, based in part on the aforementioned figures, that primary atypical pneumonia occurred more frequently in city dwellers than in residents of

rural areas. This opinion again could not be verified, as comparative statistics were unavailable.

*Past History.* The past history was carefully investigated in each case. Particular attention was given to a history of frequent colds, sinusitis, tuberculosis and previous attacks of pneumonia. All cases were interrogated regarding a previous history of tonsillectomy and adenoidectomy.

Chart 4 reveals the pertinent information gleaned from the past history. Fifty-one cases, or 15.5 per cent, gave a history of prior attacks of pneumonia, but clinically this appeared to have no bearing on the outcome of the present disease. In only 29 cases, or 9 per cent, was there a history of frequent colds or sinusitis. A positive past history for tuberculosis was extremely rare (three cases). As might be expected, approximately 29

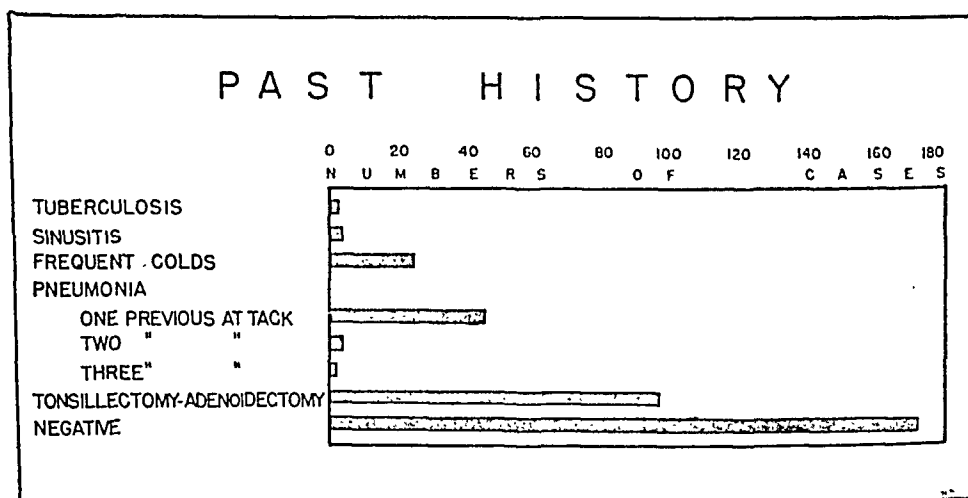


CHART 4.

per cent disclosed evidence of a previous tonsillectomy. An essentially negative history was elicited in 169 cases, representing 52.6 per cent of the series. A thorough survey of the past history exhibited no relation either to the incidence or severity of the disease.

*Onset.* The onset of primary atypical pneumonia has been variously described. Owen<sup>8</sup> noted a more sudden onset in the summer and a rather gradual onset in the winter months. Moore, Wightman, et al.<sup>12</sup> and Haight and Trolinger<sup>9</sup> observed a gradual onset in the majority of their patients. Correll and Cowan,<sup>10</sup> from their experience, classified the type of onset as sudden. Many factors have to be considered in evaluating the type of onset. Most of the symptoms existed for a considerable period preceding admission. A dry cough was present on an average of 10.3 days prior to admission. A productive cough, though uncommon, existed usually 9.5 days before admission. Sore throat antedated admission to the hospital by five days, pains in the chest by three days and fever by 2.5 days. Chills, which often denote a sudden type of onset, occurred in 98 cases, usually two days preceding admis-

sion. This latter symptom, which was evident in less than one-third of the cases, was the only one which suggested a sudden onset.

In view of the fact that practically all of the other symptoms were in evidence long before chills developed, the onset must be considered as gradual in type. This gradual onset occurred in most cases about 10 days before admission.

*Symptoms.* Chart 5 indicates the relative frequency of various symptoms which were present prior to admission. It should be stated that many of these symptoms persisted for varying lengths of time after hospitalization. The outstanding complaint, a dry cough, was present in 201 cases, or approximately two-thirds of the series. Fever was second in frequency and roughly in the same percentage. Malaise and chills occurred in about one-third of the cases. Upper respiratory infection, pain in the chest, and sore throat

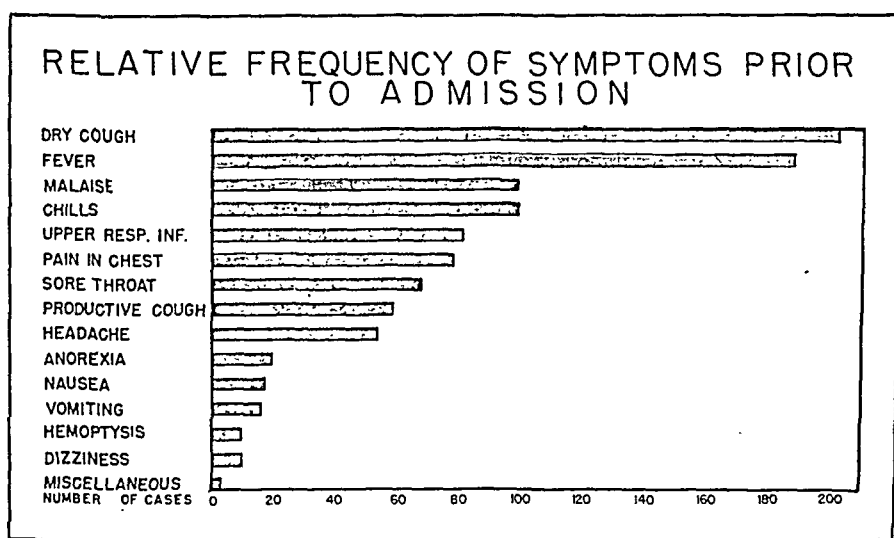


CHART 5.

throat were next in frequency and were experienced by about one-fourth of the cases. Productive cough was present in slightly less than one-fifth of the patients, another point differentiating atypical pneumonia from other types of pneumonia in which this symptom is usually present.

The relative percentages of some of these symptoms demand further mention. Chills were far more common (30.4 per cent) than one would expect, considering the usually benign course of the disease. Hemoptysis, a common occurrence in lobar pneumonia, was seen in only 3.4 per cent of the cases. About 25 per cent gave a history of recent or coexistent upper respiratory infection and the atypical pneumonic process was probably one and the same.

*Appearance of Patient.* Any appraisal of the degree of illness, based on the appearance upon admission is a matter of individual judgment, and is, obviously, not an exact index upon which to base conclusions. Observations

made on admission revealed that 174, or over half of the patients, were not considered acutely ill; 135 were regarded as moderately ill; and only 12 were deemed seriously, though not critically, ill. This latter group and some of those classified as moderately ill were the cases in which lobar pneumonia had to be excluded.

*Weight.* All patients were weighed either upon admission or shortly thereafter. Using standard weight tables as a basis, 47 per cent were found to be of normal weight and 53 per cent were equally divided between overweight and underweight. Subsequent observations revealed that weight bore no relation either to the development of the disease or to the severity of the ensuing pneumonic process.

*Physical Findings.* Some observers <sup>7, 10</sup> have reported a distinct paucity of physical findings in relation to the extent of the pathologic lesions as

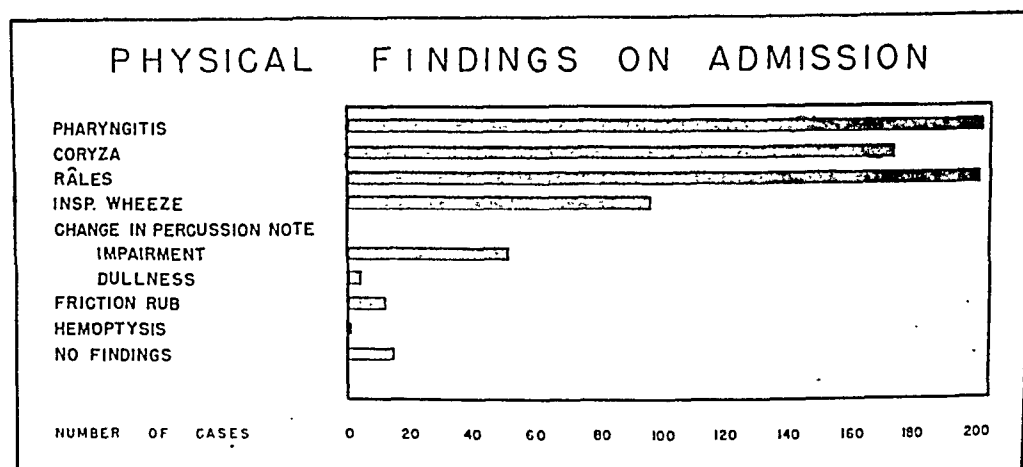


CHART 6.

demonstrated roentgenographically. Various writers have stated that early in the disease the majority of cases are characterized by the absence of clinical findings <sup>1, 5, 13</sup>; while others have remarked that the findings are minimal. <sup>6, 14, 15</sup>

In this series (chart 6) roughly two-thirds of the cases showed definite alterations from the normal physical findings. Fine or medium crackling râles were present over the affected area in 200 cases (60 per cent). Many were inaudible unless precipitated by coughing. In most of the cases these râles, though few in number, were present even on admission, if careful auscultation was carried out. Owen <sup>6</sup> reported that moist râles were the most consistent single finding in his series.

A most important physical finding, even in the absence of moist râles, was the evidence of a few high-pitched inspiratory wheezes, or sibilant râles, heard over the involved area. These wheezes were rather evanescent in character and often disappeared after a few deep inspirations, only to reappear a few hours later. This finding was observed in 29 per cent of the

cases. In view of the pathologic lesions of atypical pneumonia, this sign is of the utmost importance and has probably been overlooked by many clinicians who expected to elicit more conspicuous physical findings.

Changes in percussion note were present in relatively few cases, and this abnormality was termed simply impairment in resonance, since actual dullness was but rarely observed. This small percentage might be anticipated, as lobar distribution of the atypical process was an infrequent occurrence in this series.

Two hundred cases, or roughly two-thirds of the patients, had some degree of pharyngitis, varying from moderate injection to hyperemia. This finding was in accord with the clinical history (chart 5) which indicated

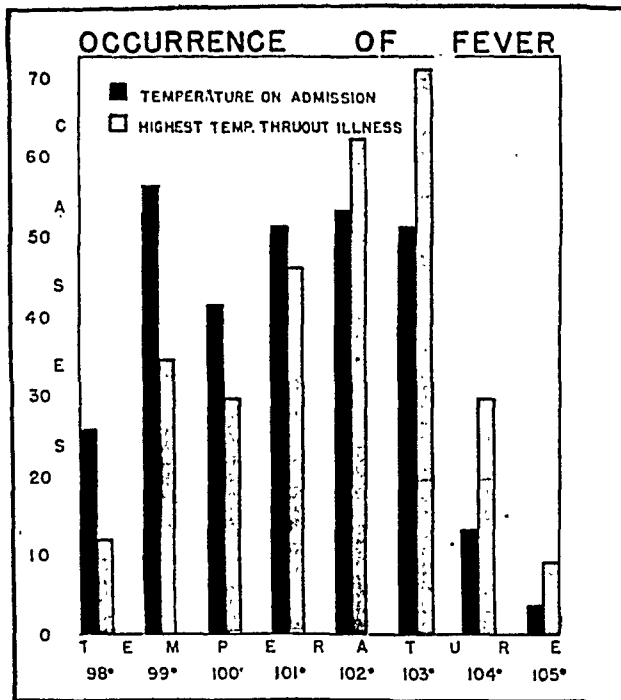


CHART 7.

that approximately that number of patients offered a complaint of sore throat or antecedent upper respiratory infection prior to admission.

*Fever.* Fever occurred in 90 per cent of the cases, whereas 10 per cent remained afebrile during their entire illness. As illustrated in chart 7, approximately 60 per cent of the cases varied between 101° and 103° F. A few cases were elevated to 104° and 105° F. This disease differs from lobar pneumonia in that a certain percentage enter the hospital with a normal temperature and develop a fever of 103° to 104° F., in 24 to 72 hours after admission.

Chart 8 graphically demonstrates the pulse rate upon admission and that encountered during the more acute stages of the disease. Seventy per cent of the cases showed a pulse rate that never exceeded 100 per minute. In

our series, atypical pneumonia was not characterized by a marked tachycardia either at the initial phase or during the peak of the illness. Tachycardia over 120 per minute and bradycardia were equally rare.

If it is recalled that in 60 per cent of the patients the temperature ranged between 101° and 103° F., it is obvious that the pulse rate was generally lower than might be expected with that degree of fever.

The same chart reveals that one-half of the patients in this series entered the hospital with a normal respiratory rate, and half of this group never exceeded this rate. Of the remainder, 45 per cent were admitted with a slight increase in respirations (22-24 per minute). During the peak of the

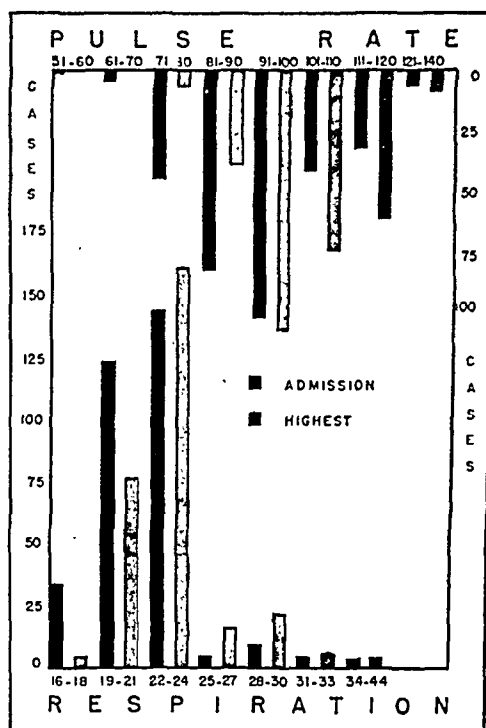


CHART 8.

illness, 50 per cent of the cases never developed a rate over 24 per minute. Unlike most other pneumonias, only 5.6 per cent, upon admission, were observed to have a respiratory rate of over 25 per minute, and only 14 per cent manifested hyperpnea during the height of the disease.

From these observations, it is apparent that in the majority of our cases, the disease was accompanied by only a moderate elevation in pulse and respiratory rates.

*Laboratory Examination.* Blood studies were performed on 261 cases (84 per cent) during the initial stage of the disease. In only 10.3 per cent was there any evidence of anemia, as determined by hemoglobin estimations. In three-fourths of the cases (74 per cent), the hemoglobin determination

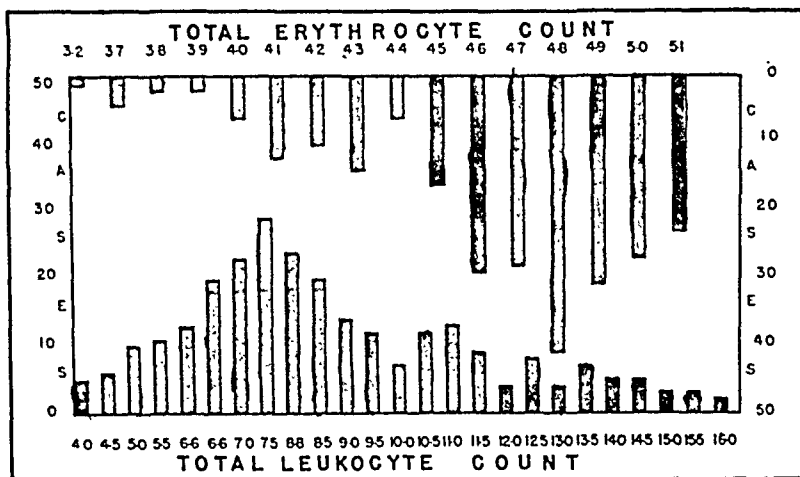


CHART 9.

was 85 per cent or more. Repeated hemoglobin estimations during the course of the disease showed no marked deviations from the initial level.

Chart 9 reveals that three-fourths of the cases had normal red cell counts (74 per cent), while only 4 per cent had counts of less than 4,000,000 per cu. mm. It is evident that there was no appreciable disparity between the hemoglobin determination and the erythrocyte count.

From the same chart, it is also apparent that the leukocyte count was normal (5,000–10,000) in most of the cases (68 per cent). A leukocytosis in excess of 10,000 per cu. mm. was present in 29 per cent, and in a small number of cases (4.4 per cent) the leukocyte count actually exceeded 15,000 per cu. mm. A leukopenia was found in only 4.4 per cent.

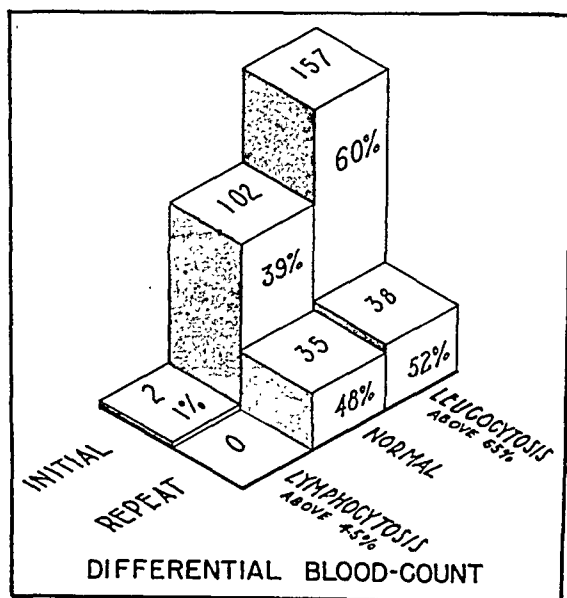


CHART 10.



From chart 10, differential counts revealed leukocytosis (over 65 per cent) in 60 per cent of the cases. A lymphocytosis (over 45 per cent) was found in only 1 per cent of the series; in the remaining 39 per cent the differential was normal. Subsequent differential counts on one-fourth of these cases revealed a persistent leukocytosis in 52 per cent. In our experience, the blood picture was one characterized by an essentially normal hemoglobin, red, and white cell count. It is also clear that the presence of leukocytosis, either absolute or relative, was no deterrent to the diagnosis of primary atypical pneumonia. A leukopenia or lymphocytosis was a rare occurrence.

*Urinalyses* were performed in all cases, and except for an occasional transitory febrile albuminuria, the findings were of no significance.

*Blood cultures* were taken in 53 cases and in all instances were reported negative.

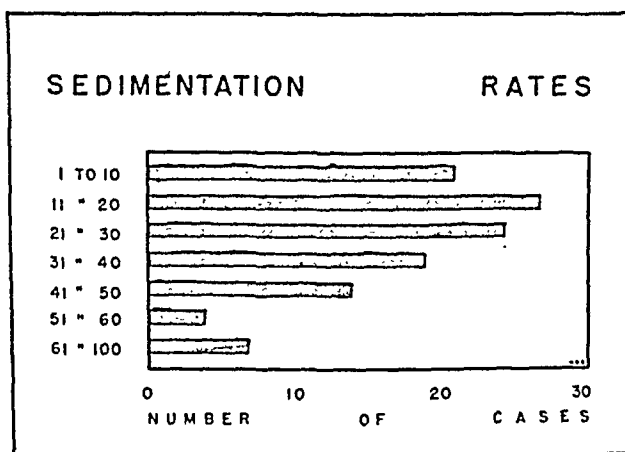


CHART 11.

*Sedimentation rates* were performed on somewhat more than one-third of the cases during the acute stage of the disease. Chart 11 indicates that more than one-third of the cases had a moderately accelerated rate (37.6 per cent), the remainder being almost evenly divided among a normal rate (18 per cent), a slightly elevated rate (23 per cent), and a rapid sedimentation rate (21.3). In the latter group were included those cases with rates in excess of 40 mm. per hour. In four of these cases, it exceeded 70 mm. per hour. Many of these rates were checked by the methods of Cutler, Wintrobe, and Westergren. Although this test was not used strictly as a guide in following a patient's progress, it was utilized as one of the criteria for discharge. In 170 cases, sedimentation rates were determined shortly before discharge, and in 154 of these cases, the rate was normal. In 16 cases the patients were discharged with a rate of 16 or above, and of this number, seven had a rate in excess of 20 mm. per hour and were discharged for emergency reasons. In our experience most of the cases had only a

moderately increased sedimentation rate, and this test was an aid in determining the optimum time for discharge. These observations tend to agree with those of van Ravenswaay,<sup>6</sup> who reported a moderate increase in the sedimentation rate in the initial stage of the disease. However, we were unable to corroborate his observation that this procedure served as an excellent guide to the progress of this disease, since in many instances, the sedimentation rate failed to parallel either the clinical or the roentgenographic findings.

*Sputum.* Sputum studies were done on the majority of cases. Fifty-one were examined particularly for evidence of *Mycobacterium tuberculosis*, but in no instances were acid-fast organisms observed.

In 135 cases, typing examinations were done to determine the presence of *Diplococcus pneumoniae*. In 117, pneumococci of no specific type were found, and in 18, type specific organisms were identified.

Table 1 indicates the predominant types.

TABLE I

Type I.....	2
Type III.....	3
Type IV.....	2
Type VII.....	1
Type VIII.....	1
Type XI.....	2
Type XIII.....	2
Type XVIII.....	1
Type XXII.....	1
Type XXVIII.....	1
Type XXIX.....	1
Type XXXIII.....	1
Number of cases with type specific organisms.....	18
Number of cases with "untypable" pneumococci.....	117
Total typings.....	135

The presence of various types of pneumococci in the sputum was difficult to evaluate. Types usually considered to be significant were found in the sputa of only 11 cases. These were Types I, III, IV, VII, VIII, and XI. The remaining seven sputa showed pneumococci of the higher numbered types. It is reasonable to assume that some of the 117 "untypable" pneumococci also belonged to the even higher numbered groups. It is also possible that these organisms may have been the cause of the pneumonic process, but when the clinical picture was considered, it was thought they were chiefly secondary invaders and any favorable results that might have occurred with sulfonamide therapy could be explained on this basis.

The question may arise as to whether some of the cases included in this series might be streptococcal in origin. The presence of pathogenic streptococci in the sputum is also difficult to evaluate. Although streptococci, staphylococci and *Micrococcus catarrhalis* were frequently found in the sputum, a pure culture of streptococci was obtained only in five instances. The benign clinical picture, the roentgenographic findings along with the total absence of complications, such as empyema, all were against this diagnosis. It is still possible that a few of these cases may have been unusual

streptococcal pneumonias, but such a diagnosis could not be substantiated by laboratory or clinical findings.

### ROENTGENOGRAPHIC FINDINGS

A brief review of the pathology of atypical pneumonia is necessary before a proper evaluation of the roentgenographic changes can be made. Inasmuch as there were no fatalities in our series, original comment on the pathologic lesions of the disease cannot be offered. Relatively little has been published about the pathologic aspects of atypical pneumonia. Needles and Gilbert,<sup>7</sup> on one autopsy, noted on gross examination evidence of hilar node enlargement and a bronchial tree filled with creamy, viscid, yellow exudate which, when scraped away with difficulty, left a hemorrhagic bronchial mucosa. They also found hundreds of minute areas of infiltration resembling the gross picture of miliary tuberculosis, but the cut section was grayish pink, and scattered throughout the lung were nodules resembling bronchopneumonic consolidation. In summation, the picture was one of miliary pneumonitis, purulent bronchitis, and bronchiolitis. Microscopic examination revealed elongated, tortuous pulmonary alveoli lined with cuboidal epithelium. These cuboidal alveolar lining cells often projected into the bronchial lumina which were invariably filled with a purulent exudate essentially composed of polymorphonuclear elements. Fibrin was not noted. The interstitial tissues were greatly thickened, and the septa were packed with inflammatory cells of the round, wandering or plasma cell types. There was scattered loss of bronchial mucous membrane. The appearance was essentially one of bronchitis and interstitial pneumonia, and the pattern as a whole was that of proliferation and exudation.

Golden, quoted by Owen,<sup>8</sup> reported similar findings on gross examination, but stressed the point that both the peribronchial cellular infiltration and the associated congestion and edema of the lung tissue were essentially free of pus cells. Instead of the usual polymorphonuclear infiltration seen in pneumonias, these areas showed a predominance of lymphocytes, plasma cells and monocytes. If secondary infection occurred, hemorrhage, polymorphonuclear leukocytes, and fibrin formation became prominent, but failed to obscure the fundamental process.

Campbell et al.,<sup>16</sup> in their single necropsy, noted approximately the same findings as reported by the other investigators but observed evidence of atelectasis manifested by reduction of lung volume and decrease in the size of the alveoli.

Since the pathological sequence of events is probably a proliferative bronchitis, bronchiolitis, and interstitial pneumonitis, there must be a time when actual disease changes are present, though invisible by roentgen-ray. Showacre and his co-workers<sup>17</sup> concluded from their observations that an early film read as a negative does not rule out developing atypical pneumonia. When roentgenographic changes are evident, they may represent merely

endobronchial proliferation, peribronchial nodulations, or interstitial infiltration, or they may be the result of any combination of these processes.

The roentgen changes produced by this pulmonary reaction were multi-form in character. These shadows often assumed the form of a veil-like extension projecting from the hilus, or were manifested by cloudy mottling or irregular areas of uneven density, varying in size from that of a pin point to nearly that of a dime. The typical lack of homogeneity of these shadows frequently made it difficult to delineate actual lobar involvement. Now and then, a dense form of consolidation not unlike that seen in lobar pneumonia was observed with distinct lobar demarcation.

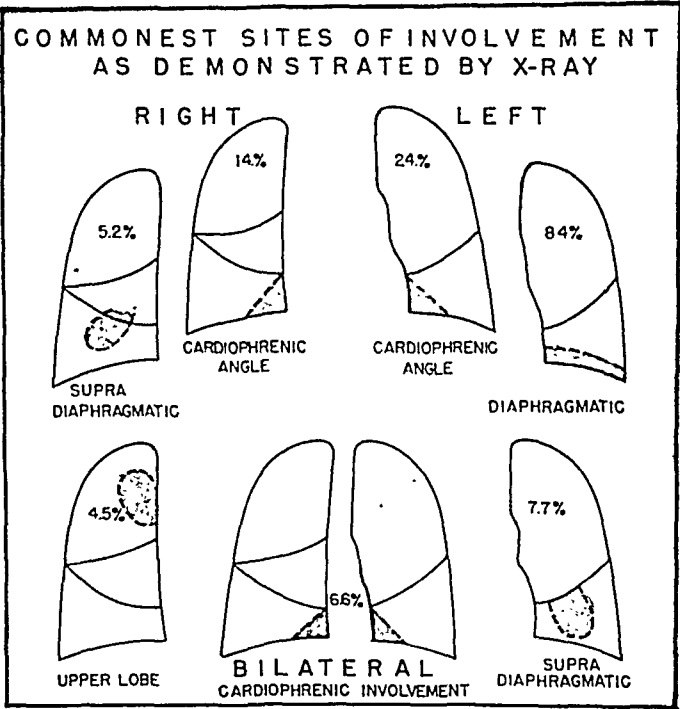


CHART 12.

In our survey, 17 more or less distinct areas of involvement were observed.

Roentgenograms illustrating the characteristic type of involvement in the six commonest sites are shown in figure 1.

Chart 12 portrays the pulmonary areas which were most frequently involved with an atypical pneumonic process. The appended table (2) reveals the areas of lessened incidence. It is apparent from chart 12 and table 2 that atypical pneumonia had a distinct predilection for involvement of the lower lung fields (79.9 per cent), and in this distribution, lesions of the dependent portion of the left lung predominated (41.6 per cent). It should also be pointed out that lesions of the left lung were far more common (48.1 per cent) than involvement of various regions of the right lung (34.8 per

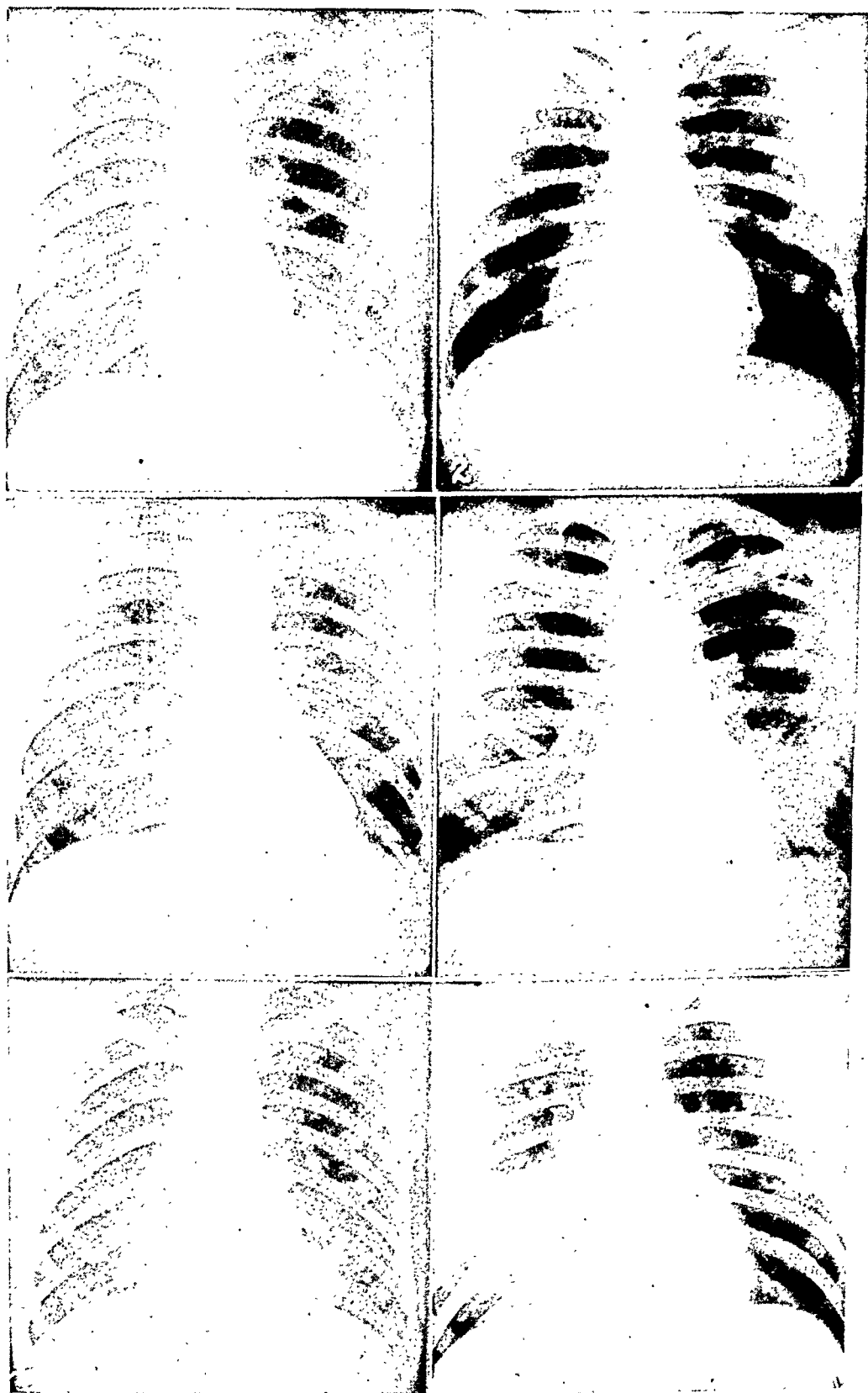


FIG. 1. (1) Left cardiophrenic lesion. (2) Right cardiophrenic lesion. (3) Left diaphragmatic involvement. (4) Left supradiaphragmatic lesion. (5) Bilateral cardiophrenic involvement. (6) Right supradiaphragmatic lesion.

cent). Bilateral processes were observed in only 12.6 per cent, and these were confined almost entirely to the lower lung fields.

Inasmuch as the pneumonic process only rarely involved an entire lobe, it seemed justifiable to use a more descriptive method in designating the site of involvement.

In considering pneumonias of the lower lung fields, it seemed more practical to designate the lesion according to its relationship to the cardiophrenic angles, the diaphragms, or the costophrenic angles. It should be pointed out that a cardiophrenic lesion may extend across the diaphragm to form a diaphragmatic lesion. All lesions of the lower lung field, not impinging directly upon the diaphragm and not distinctly lobar in distribution, were termed supradiaphragmatic. This designation was considered more accurate than any attempt to assign lobes in a poorly demarcated type of lesion.

In most of our cases, the lesion appeared to originate in the hilus and fan outward usually into the lower lung fields. When the lesion spread downward, it frequently extended along the cardiac borders or in a path posterior to the heart.

TABLE II

Less Frequent Sites of Involvement as Seen by Roentgen-Ray

Left hilar zone . . . . .	3.9%
Right diaphragmatic region . . . . .	3.4
Right costophrenic region . . . . .	3.4
Bilateral diaphragmatic regions . . . . .	3.2
Bilateral supradiaphragmatic regions . . . . .	2.5
Left upper lobe . . . . .	2.6
Right hilar zone . . . . .	2.3
Left costophrenic region . . . . .	1.5
Right middle lobe . . . . .	1.5
Bilateral hilar zones . . . . .	.3
Miscellaneous . . . . .	4.5

It was also difficult at times to attach the proper term to those lesions emerging from the hilus and radiating towards or into the upper lobes, and to those confined essentially to the hilar region. In this latter category, only those cases were included in which the infiltration extended no further than the pulmonary midzones. By lobar involvement was meant those lesions which extended beyond the midzones into the periphery of the upper lobes (figure 2). It should be pointed out that the atypical process rarely occupied the entire lobe, and the density was seldom so marked as that seen in pneumococcic pneumonia. Furthermore, none of these areas was distinct in the same sense as that found in typical lobar consolidation.

Table 3 shows the incidence of atypical pneumonic involvement in our series, utilizing the aforementioned terminology, as compared with similar series using the lobar type of designation.

Roentgenographic findings disappeared on the average in about 18 days, although in seven cases, roentgenographic abnormalities persisted for 60 days or more. One case cleared in three days. In evaluating the time required for clearance of roentgenographic manifestations, consideration should be given to the history of the onset which in many cases antedated the

admission to the hospital by several days. Undoubtedly, if it were possible to roentgen-ray all cases at the onset of initial symptoms, the length of time required for clearance would be even longer than was actually determined. In other words, the time required for roentgen clearance is dependent on the stage of the disease upon which the original roentgenogram was taken.

It has been postulated that the diagnosis of atypical pneumonia is made by the roentgen-ray.<sup>7, 13</sup> In a corroborative sense, this statement is true, but it is also possible with the aid of a careful history, thorough physical examination, and proper evaluation of laboratory work, to make a reasonably

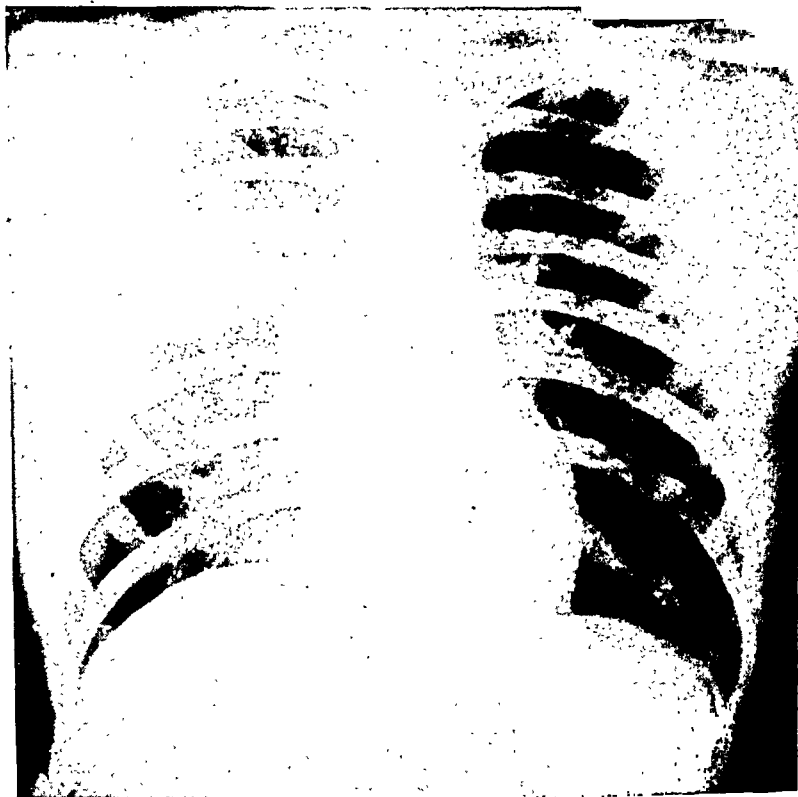


FIG. 2. Lobar involvement.

correct diagnosis without the aid of the roentgen-ray. It should be recalled that the roentgen findings, though relatively characteristic of this disease, are not pathognomonic, since other pathological processes, particularly pulmonary tuberculosis, may simulate the condition. It is an indisputable fact that the roentgen-ray is a most valuable adjunct, but the diagnosis should not be made solely by this method.

#### COURSE AND TREATMENT

The treatment of atypical pneumonia is governed by the particular phase of the disease with which the physician is dealing. The disease may be divided into three stages: acute, subsiding, and convalescent.

The acute stage was manifested by at least one of the following findings: persistent fever, abnormal chest signs, characteristic roentgenogram, or the presence of toxemia. Once this stage had been determined, the therapy was either symptomatic or chemotherapeutic. Bed rest was essential at this time. A soft bland diet was routinely prescribed and efforts were made to maintain a fluid intake of at least 3000 c.c. per day. The common expectorants were ordinarily indicated and steam inhalations often afforded relief. Symptoms resulting from pharyngitis and coryza responded to the usual remedies. Antipyretic drugs were seldom utilized.

TABLE III

	Dingle <sup>15</sup>	Owen <sup>8</sup>	Wightman <sup>12</sup> Showacre Moore	Present Series		
Right Lung						
Upper lobe	6.7	5.5	6.	5.		
Middle lobe	2.5	3.5	1.	1.5		
Lower lobe	29.8	36.	33.	26.	Cardiophrenic	14.
					Supradiaphragmatic	5.2
					Diaphragmatic	3.4
					Costophrenic	3.4
						<u>26.0</u>
Entire right lung			1.			
Hilus alone	9.1			2.3		
Left Lung						
Upper lobe	5.6	5.	2.5	2.6		
Lower lobe	33.7	50.	43.	41.6	Cardiophrenic	24.
					Diaphragmatic	8.4
					Supradiaphragmatic	7.7
					Costophrenic	1.5
						<u>41.6</u>
Entire left lung			2.			
Hilus alone	3.5			3.9		
Both lungs (lower lobes)	6.0		6.5	12.6	Cardiophrenic	6.6
					Diaphragmatic	3.2
					Supradiaphragmatic	2.5
						<u>12.3</u>
Hilus alone				.3		
Other combinations	3.2		5.	4.5		

Dry cough was often quite persistent, lasting several weeks. Codeine occasionally was necessary, but its use was limited, since it was felt that moderate cough was beneficial physiologically. This cough, in many cases, responded to bed rest alone. In patients showing pronounced bronchial spasm, ephedrine sulfate was beneficial, and in cases with marked tenaciousness of the sputum, potassium iodide was worthy of trial. At times, pleural pain was of such severity as to warrant the use of codeine or even morphine.

The other mode of attack was through the medium of sulfonamide administration. The writers are fully cognizant of the almost universally reported poor results obtained with sulfonamides in this disease.<sup>5, 7, 11, 16</sup> The



drug was not given routinely as Thompson<sup>14</sup> did, but only in those cases exhibiting any one of the following five conditions:

1. Marked febrile reaction of at least 72 hours' duration.
2. Leukocytosis.
3. Clinical pulmonary findings and roentgenogram suggestive of lobar distribution.
4. Failure to show appreciable response to symptomatic management.
5. Suspicion of secondary bacterial invasion, suggested by identification of type specific pneumococci from sputum.

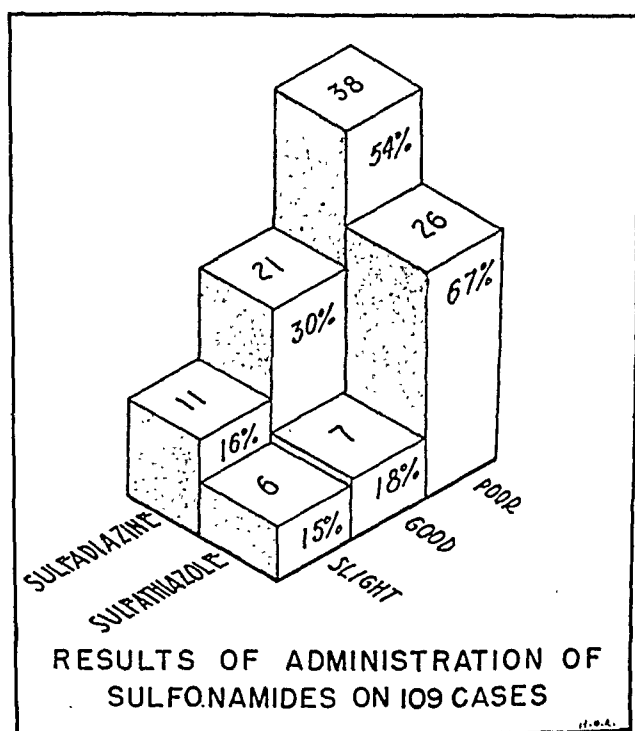


CHART 13.

Our results are depicted in chart 13. Seventy cases were treated with sulfadiazine in the usual dosage. In 38 cases (54 per cent), the result was regarded as poor. In the other 32 cases, 11 showed slight response to the drug, and in 21 cases (30 per cent), the results varied from good to excellent. The results from sulfathiazole were not so satisfactory. Of 39 patients treated with this drug, poor results were obtained in 26 cases (67 per cent), slight improvement in six cases (15 per cent), and good or excellent results in seven cases (18 per cent). In other words, in 109 cases treated with sulfonamides, a good to excellent result was obtained in 28 cases (25 per cent). This is at variance with reports of many other observers.<sup>5, 7, 11, 16</sup> Although atypical pneumonia per se may not often respond to chemotherapy, it is fair to conclude that the disease is frequently complicated by secondary

bacterial invaders against which sulfonamides exert a specific effect. In most cases, the acute stage did not exceed 10 days. As seen in chart 14, the majority were afebrile within five days. In a small number of cases, a temperature of 99.2° to 100° F. persisted for several days to several weeks, occasionally for several months.

The second or subsiding stage was characterized by the absence of fever for 72 hours, the lessening of most symptoms, evidence of clinical clearing of the chest, and roentgenographic changes suggesting resolution. However, the management of this stage occasionally required symptomatic treatment. The dry cough, so troublesome in the acute stage, persisted in few cases and again, simple expectorants, rather than codeine, were indicated. As a further mechanism in the therapy of persistent cough, mild-to-moderate controlled exercise was utilized, and it was felt that this procedure might have been instrumental in reducing the incidence of bronchiectasis. Augmenting pulmonary aeration was particularly indicated, because of the

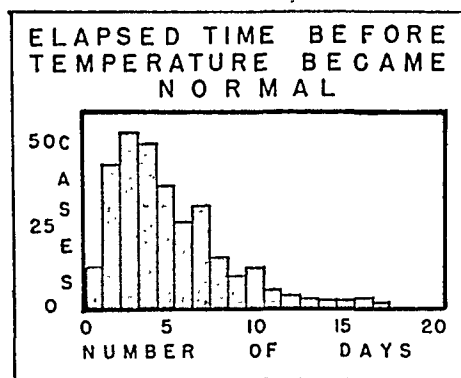


CHART 14.

pathology of this disease. The duration of the subsiding stage was usually between 10 and 21 days.

The final or convalescent stage was reached when the roentgenogram showed complete or nearly complete resolution, the chest findings were negligible, and the patient was asymptomatic, except for varying degrees of weakness and decreased exercise tolerance. Chart 15 indicates respectively the number of days required for the roentgenogram to become clear, the number of days of normal temperature prior to discharge, and the duration of hospitalization. As a rule, the roentgenograms returned to normal much more slowly than did the temperature and physical findings.

As mentioned before, the average time required for roentgen clearance was 18 days. The peaks shown in chart 15 are the result of routine roentgenograms at weekly intervals over a period of four weeks.

The second portion of the chart indicates that on the average the patient was hospitalized for 17 and one-half days after the subsidence of fever. If it is recalled from chart 14 that in most cases the temperature became normal

within five days, the average patient would require a hospital stay slightly in excess of three weeks.

From the third portion of the chart, it is apparent that most patients were hospitalized between 20 and 30 days, averaging 27.5 days. Further hospitalization of roughly 10 days was necessary following roentgenographic clearance because of increased sedimentation rates and delayed convalescence.

Although the convalescent period averaged between 10 days and two weeks, some patients required three to four weeks, and a few needed as much as six weeks or more before recovery was complete. In other words, certain cases presented distinct differences in their ability to combat this disease. The treatment in this stage was graduated exercises and occupational therapy.

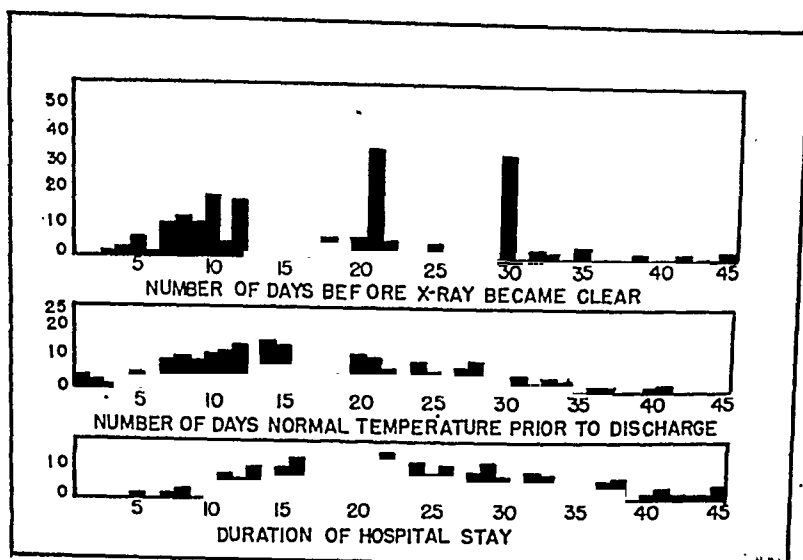


CHART 15.

Repeated attacks of coryza and mild nasopharyngitis were not infrequent, and some of our patients seemed to manifest an increased susceptibility to upper respiratory infections. Particularly was this true in cases which had delayed resolution. Paranasal sinusitis, though not considered a complication, occurred in several cases, but the pneumonic process was not a contraindication to treatment.

A few cases in the subsiding or convalescent stage developed vague abdominal distress. Rarely, this pain became localized in the right lower quadrant. In about eight of these cases, surgical consultation was necessary, and appendectomy was performed in two. This syndrome, often quite persistent, appeared to be independent of the pneumonic process and usually cleared spontaneously.

The following criteria were used in arriving at the optimum time for discharge:

1. Continued normal temperature and absence of pertinent symptoms.
2. Normal chest findings.
3. Roentgenogram within essentially normal limits.
4. Normal sedimentation rate and blood picture.
5. Satisfactory exercise tolerance.
6. Freedom from complications.

By an essentially normal chest film was meant the absence of frank infiltration. The presence of residual prominent bronchial markings, small areas of pleural thickening or diaphragmatic adhesions, were not considered of clinical significance.

*Incubation Period and Contagiousness.* No conclusion could be reached as to the incubation period of this disease. Various other writers<sup>6, 16</sup> have speculated as to the length of this period, but in our opinion, it is still undetermined.

It is interesting to note that only three members of the medical staff and one nurse contracted the disease during the period included in this study. Despite repeated exposure, no ward attendants employed on the pulmonary service developed the disease.

#### COMPLICATIONS

In our series, atypical pneumonia was attended by few complications. Of the 321 cases, only 24 (7 per cent) developed a condition which could be so classified.

Symptomatic pleurisy, which is exceedingly common in lobar pneumonia, was rarely observed as a complication. Only seven cases (2 per cent) could be classified as developing frank clinical evidence of pleurisy as a complication. Obviously, many cases had radiographic evidence of pleurisy, manifested by cloudiness of the costophrenic angle or irregularity of the diaphragm, but this was considered an integral part of the picture of the acute disease process and, therefore, not to be regarded as a complication. The type of pleurisy noted roentgenographically was simply a thickening of the pleura as a result of the antecedent pneumonic process. No gross effusion or empyema occurred. This infrequent incidence of wet and dry pleurisy was unusually small in comparison with the incidence reported by other investigators, notably van Ravenswaay,<sup>6</sup> who noted an incidence of 9.7 per cent in pleural effusions alone, and Owen,<sup>8</sup> who observed this complication in 4 per cent. One of Owen's cases developed empyema.

Complications arising from the associated upper respiratory infection were also rare. Only three cases of otitis media, two cases of sinusitis, two cases of conjunctivitis, and one case of laryngitis were observed. Bronchiectasis was also an extremely rare result of the pathological process. This condition was proved to be an actual complication in only two cases. Lipiodol injections were performed in four other suspicious cases, but the bronchograms were considered negative. Blades and Dugan<sup>18</sup> have re-

ported the occurrence of a condition resulting from atypical pneumonia, which they termed pseudobronchiectasis. These investigators considered the lesion to be temporary in most of these cases, returning to normal in a period of four to six weeks. It is possible that the two cases we reported may have been of this type, but in the period of observation permitted, the diagnosis of permanent changes in the terminal bronchial tree was made.

Other uncommon complications were hematuria in one case, persistent headaches of undetermined etiology in two cases, and a recurrence or recrudescence of primary atypical pneumonia in three cases.

### ELECTROCARDIOGRAPHIC ABNORMALITIES

Cardiac complications in lobar pneumonia are well-known. Spühler,<sup>19</sup> in routine investigations of the cardiovascular system in lobar pneumonia, found a considerable percentage with cardiac changes. His studies indicated that many of these alterations were mild, reversible myocardial changes evidenced by electrocardiographic and roentgenographic findings. In contrast to these milder cases, irreparable damage, particularly to the conduction system, was observed in other cases. In Spühler's experience, pericarditis was a fairly frequent complication, originating, in his opinion, by extension or metastatic spread.

Early in the present series, these observations were substantiated in a case of lobar pneumonia involving the left lower lobe. During the acute stage of this case, gallop rhythm and a transitory to-and-fro pericardial friction rub were heard. Pericarditis and myocarditis were suggested by the electrocardiogram, manifested by elevated RST segments in all leads; a negative T-wave in the chest lead, and a partial auriculoventricular block with PR interval of 0.32 second. Auriculoventricular conduction time returned to normal, but the elevated RST segments and negative T<sub>4t</sub> persisted during a three-month observation period. During the latter period of hospitalization, the patient was able to tolerate mild activity. Serial electrocardiographic tracings on this case are shown in figure 3.

Similarly, electrocardiographic abnormalities were observed in one of our earliest cases of atypical pneumonia. These findings served as a stimulus to further investigation of electrocardiographic changes in this disease process. A short time prior to our observations, Fuller and Quinlan<sup>20</sup> and Wolff<sup>21</sup> reported similar changes associated with cases of atypical pneumonia. In 100 cases studied by Fuller and Quinlan,<sup>20</sup> abnormal changes in the RST segments were observed in 11 cases and an inverted T<sub>4t</sub> was noted in five cases. In their series all of these variations reverted to normal.

Wolff<sup>21</sup> noted almost identical abnormalities in the RST segment in three cases of atypical pneumonia and considered this evidence pathognomonic of pericarditis, despite the absence of clinical findings. Three additional cases of pericarditis associated with primary atypical pneumonia were recently described by Finkelstein and Klainer.<sup>22</sup> The changes in the RST segments in their cases were essentially the same as those noted by the other observers,

and closely resembled the electrocardiographic findings in our cases. In their experience the abnormalities of the RST segment disappeared within a period of three months.

In the aforementioned case (No. 2) typical roentgenographic evidence of a left cardiophrenic type of involvement was present, with only minimal clinical evidence of pneumonia. However, the pneumonic process ran a rather chronic course with persistent low-grade fever of six months' duration. The roentgenogram cleared in a period of about two months. During the fifth month of his illness, the patient experienced vague precordial pains unassociated with dyspnea, cardiac dilatation, murmurs or pericardial friction. Serial tracings were made and figure 4a shows the electrocardiographic

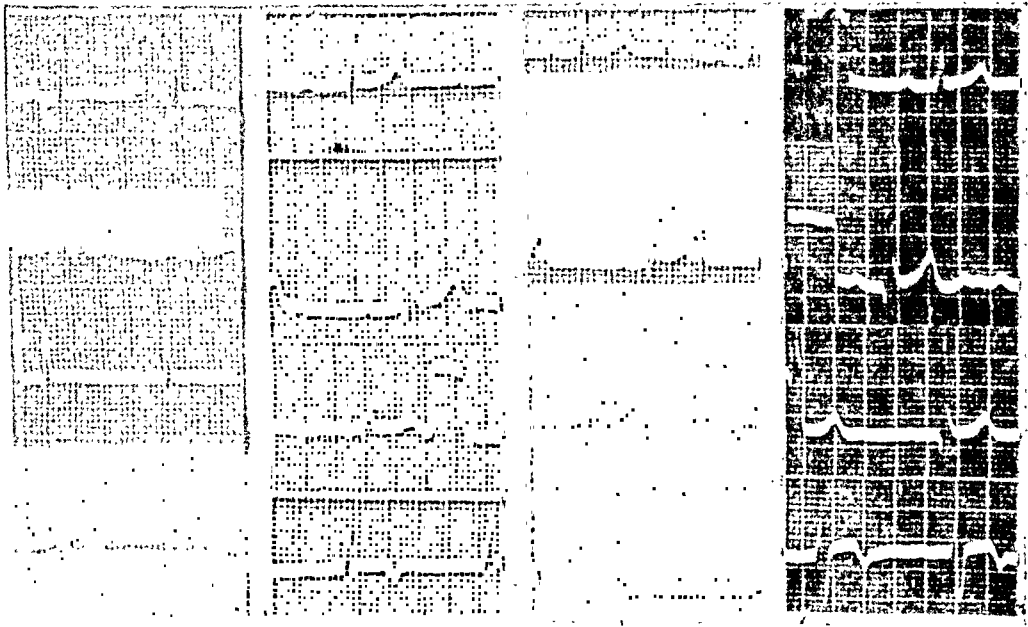


FIG. 3. Electrocardiogram in a case of lobar pneumonia showing abnormalities suggesting pericardial and myocardial involvement.

changes noted in this case. These findings suggested myocardial or pericardial involvement, or both, as evidenced by a negative  $T_{4r}$  and a prolonged PR interval. The changes in this case were reversible, and the electrocardiogram returned to normal in a period of about six weeks. Simultaneously, the patient showed clinical improvement and was returned to duty.

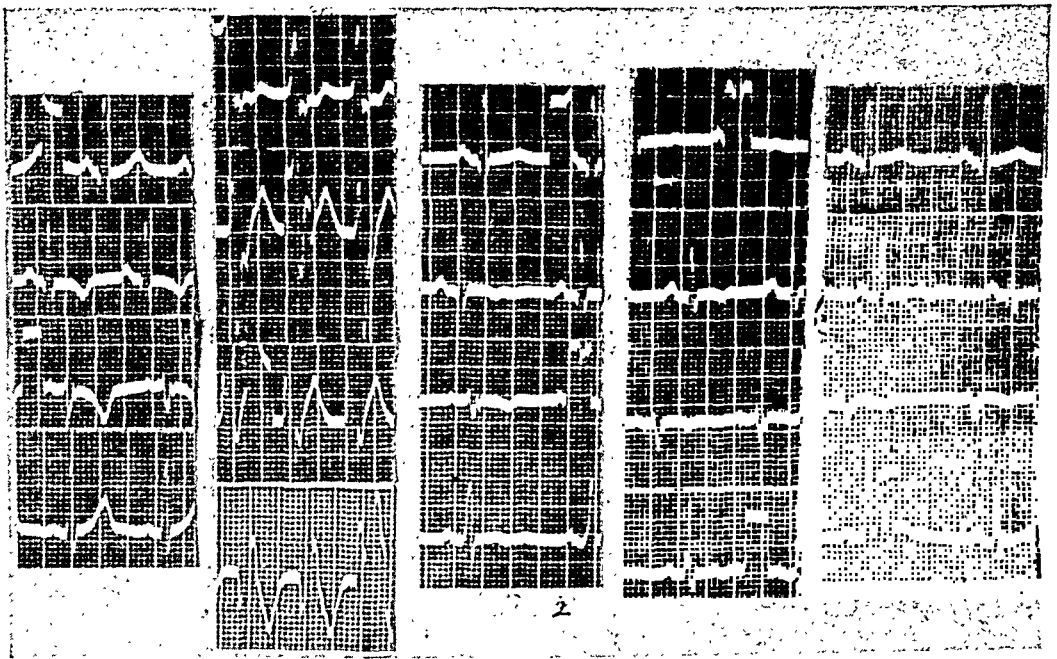
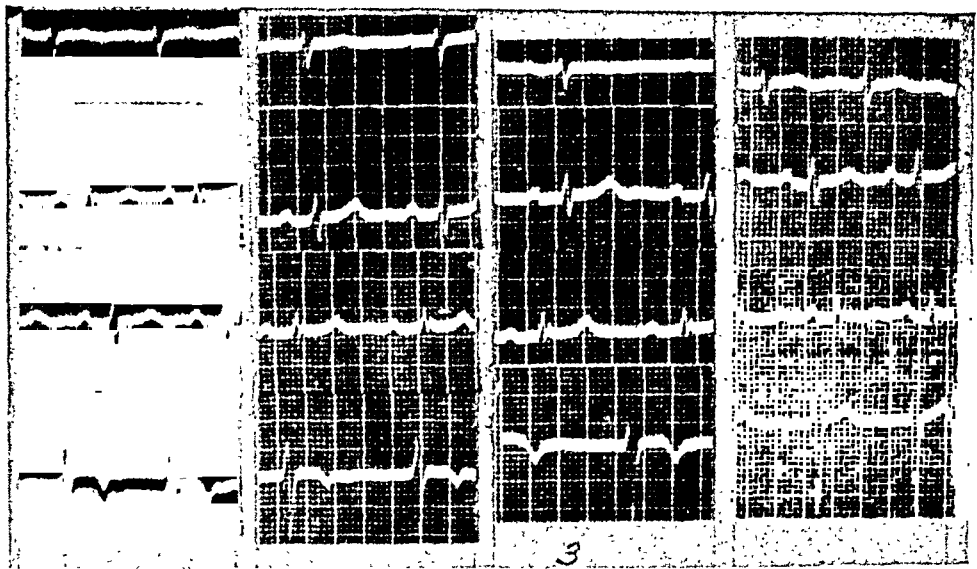
Following this initial case, electrocardiograms were done on 63 other cases of atypical pneumonia. Forty cases were studied routinely, utilizing serial tracings, whereas in the remainder, electrocardiograms were done because of either a persistent low-grade fever, unduly delayed roentgen clearance or a prolonged convalescence. Twelve of the cases studied showed electrocardiographic evidence suggestive of myocardial and pericardial involvement. Only two of these patients presented clinical evidence suggesting a cardiac abnormality.

9/30/43

10/9/43

11/1/43

11/8/43



11/3/43

12/30/43

1/24/44

2/14/44

2/28/44

FIG. 4. a (above) and b (below).

Brief case histories and serial electrocardiograms illustrate the typical findings in three other cases (figure 4b, figure 5, a and b).

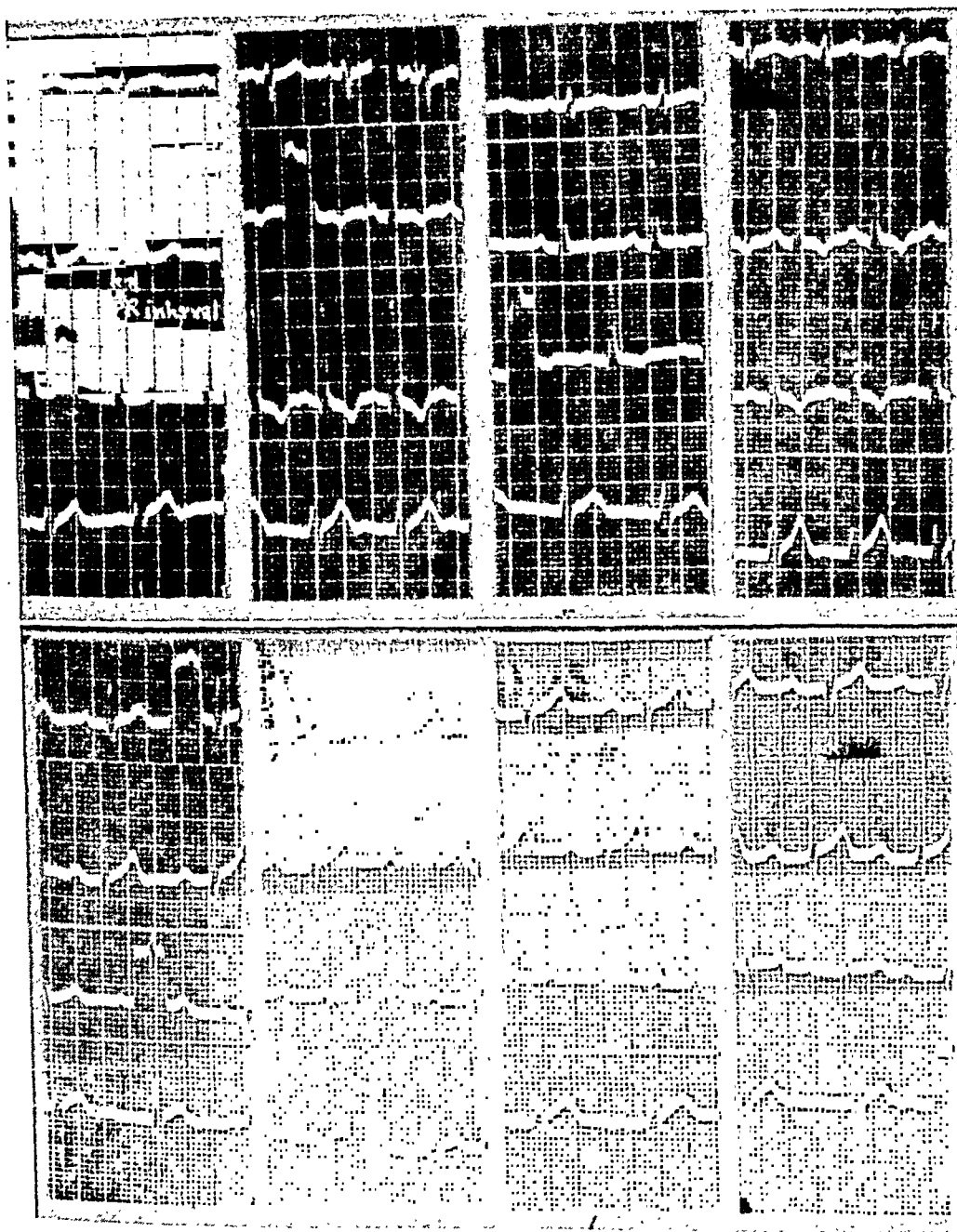
Case 3, an obese male of 22, was admitted to the hospital with a history of sore throat, fever, malaise, and a dry cough of three days' duration. Physical examination showed only a few subcrepitant râles at the right base, and the roentgenogram revealed minimal infiltration at the right cardiophrenic angle. The latter cleared in two weeks, but a routine electrocardio-

11/2/43

12/27/43

2/14/44

3/20/44



1/7/44

1/14/44

2/3/44

3/28/44

FIG. 5. a (above) and b (below).

gram suggested an active process in the pericardium and myocardium, which reverted to normal only after a period of four months.

Figure 4b (case 3) shows inverted T-waves in the second and third leads in the first set of tracings, nodal tachycardia and bundle branch block in the second, negative T<sub>2</sub>, T<sub>3</sub> and T<sub>4f</sub> in the third, inverted T-waves in all



leads in the fourth, and a reversal towards the normal in the last set of tracings.

The next, case 4, was first observed as an out-patient in the medical clinic, complaining of a non-productive cough of two weeks' duration associated with weakness, cardiac palpitation, and dyspnea on exertion. Clinically, the lungs were clear and the heart negative, except for a moderate tachycardia (100 per minute). Moderate cyanosis was present. An electrocardiogram at this time was normal. A chest film showed a heart of normal size, along with a minimal mottling of the right supradiaphragmatic region. The patient was admitted to the hospital, and the pneumonic process cleared both clinically and radiographically in three weeks, under symptomatic management. The electrocardiograms, however, as depicted in figure 5a, showed changes in  $T_2$  and  $T_3$  which persisted throughout a four month period of observation. During the latter three months in the hospital this patient was ambulatory, afebrile, showed a normal sedimentation rate and except for tachycardia and slight exertional dyspnea, presented no other clinical evidence of cardiac involvement.

The next, case 5, a colored male of 24, was admitted with symptoms suggesting atypical pneumonia, confirmed by roentgenographic evidence in both cardiophrenic angles. This patient was not acutely ill, but exhibited a low-grade fever of 45 days' duration. Roentgen findings required 60 days for clearance. Except for a slight transient precordial pain, there were no symptoms referable to the heart. Cardiac examination was entirely negative. In view of persistent low-grade fever and slow roentgen clearance, along with the complaint of precordial pain, an electrocardiogram was taken.

Figure 5b illustrates the RST elevations observed in this and similar cases. However, in addition to these changes, this patient presented a persistent partial A-V block (PR interval .32 second). Repeated tracings taken over a period of three and one-half months showed no tendency to revert to the normal.

The remaining eight cases showed similar electrocardiographic changes consisting of elevation of the RST segments, inversion of the T-waves, or a disturbance in A-V conduction.

In summation, 12 (3.7 per cent) of the 321 cases studied revealed electrocardiographic deviations from the normal, which consisted essentially of elevation of the RST segments, flattening or inversion of the T-waves in one or more leads, or changes in auriculoventricular or intraventricular conduction. Seven of these cases showed clinical and electrocardiographic reversal to normal, whereas the other five cases showed irreversible changes which persisted throughout a three month observation period. It is important to note that all cases showing electrocardiographic abnormalities were associated with atypical pneumonia limited to the lower lung fields. Seven of these cases occurred with atypical processes involving the left lower lung field, whereas the other five cases developed in connection with disease of the lower right lung. Most of these cases showed atypical processes of

the cardiophrenic type of distribution. It is possible that the proximity of the lesion to the heart may have had a causal relationship to these electrocardiographic changes.

### DISCUSSION

For many years any deviations from normal in the RST segments were regarded as unequivocal evidence of organic heart disease. In recent years it has been definitely established that a wide variety of causes, other than organic heart disease, may produce changes in this terminal segment of the tracing. Some of these conditions which have been shown to produce changes in the RST segment or abnormalities in the T-wave are: neurocirculatory asthenia<sup>23, 24</sup>; hyperventilation with alkalosis<sup>25</sup>; effects of various drugs, as digitalis, atropine, mechohyl, prostigmine, epinephrine, nicotine, ergotamine and the sulfonamides; metabolic disorders, as hypothyroidism<sup>26</sup> and hypoglycemia<sup>27</sup>; and blood dyscrasias, i.e. pernicious anemia and acute blood loss.<sup>28</sup> In addition to these causes, various types of infection are capable of altering the RST segment, e.g., rheumatic fever, streptococcal and pneumococcal disease, diphtheria, mumps,<sup>29</sup> virus diseases (produced experimentally,<sup>30</sup> trichiniasis,<sup>31</sup> and spirochetosis icterohemorrhagica (Weil's disease)).<sup>32</sup>

Lastly, any discussion would be incomplete which failed to include the various forms of organic heart disease that typically affect this portion of the tracing, namely, myocardial ischemia (coronary disease), acute and chronic constrictive pericarditis, acute cor pulmonale,<sup>33</sup> and dissecting aneurysm. A few other less significant conditions could be mentioned but it was felt that they were of insufficient importance to warrant special consideration.

All of the above conditions were considered in determining the significance of these various RST changes. Though neurocirculatory asthenia was a possible clinical diagnosis in some of these cases, the changes in the RST segments were not merely confined to T<sub>2</sub>, as reported by Graybiel and White,<sup>23</sup> Merritt<sup>24</sup> and others, but existed usually in several leads. Furthermore, the changes reported in our cases occurred when the tracings were taken in a recumbent posture, whereas those changes reported in neurocirculatory asthenia were noted only when the tracing was taken in a sitting position. Any possible effects of hyperventilation, with resulting alkalosis, can quickly be eliminated, as very few of our patients showed rapid respiratory rates (chart 8). The effect of drugs upon the electrocardiogram can similarly be discounted, as none of our patients received any drugs, with the exception of sulfonamides, that might have an effect on the electrocardiogram. The influence of sulfonamides upon the electrocardiogram deserves a word of mention. It has been shown by Simon<sup>34</sup> that this drug is capable of producing an interstitial myocarditis with localized necrosis in patients dying of sulfonamide intoxication. Inasmuch as only four of our cases in this group received the drug and these cases failed to show any

other evidence of sulfonamide toxicity, the changes reported could not be explained on this basis.

Metabolic disturbances too were considered but pertinent investigation failed to reveal diagnostic evidence of that type of disorder. Blood dyscrasias were not a factor in our series (chart 9).

As mentioned above, changes in the RST segments commonly occur with many infections. Casual observation might lead one to consider these cases actually rheumatic fever with an associated pneumonitis and concomitant myocarditis and pericarditis. It was felt that this possibility could be adequately excluded for the following reasons. First, none of the reported cases fulfilled even the minimal criteria for the diagnosis of rheumatic fever as set up by Jones.<sup>35</sup> It is true our cases presented electrocardiographic evidence suggesting myocarditis but all lacked the supporting clinical findings (significant cardiac murmurs, pericardial friction rubs, etc.) necessary for inclusion under the principal major manifestation. The other major manifestations, i.e., arthralgia and peri-arthritis, were conspicuously absent. Furthermore, of the minor manifestations only precordial pain was observed and that symptom rarely. Second, none of these cases developed signs of congestive failure, a finding frequently noted in connection with rheumatic pneumonitis. Third, none of our patients at the time these changes appeared developed a significant anemia, leukocytosis, or an appreciably elevated sedimentation rate, commonly seen with rheumatic fever. Fourth, none of our cases in this group gave a previous history of rheumatic fever. Lastly, the relatively non-toxic appearance of the patient and the completely benign clinical course essentially precluded this diagnosis.

The possibility that streptococcal or pneumococcal infection was the basis for these electrocardiographic changes was not likely. All of our cases presented a relatively benign clinical picture and at the time the RST changes were noted the leukocyte counts were within normal limits. It was felt that the mild character of the manifestations and the absence of leukocytosis militated against a streptococcal or pneumococcal origin for these findings. Diphtheria, trichiniasis and spirochetosis icterohemorrhagica could be quickly dismissed as possibilities, because none of the patients showed any of the characteristic findings of these diseases.

Changes in the RST segments, as a result of virus infections, would have to be considered more seriously as a diagnostic possibility. Pearce and Levine<sup>30</sup> have experimentally produced the pathological picture of myocarditis in rabbits by the intratesticular injection of various viruses. These investigators performed electrocardiograms during the early and acute stages of the disease and observed changes in the RST segments with or without disturbances in conduction in 88 per cent of those animals showing evidence of myocarditis at autopsy. Recently Wendkos and Noll<sup>29</sup> reported changes in the RST segment and a prolonged PR interval in a single case of mumps. These observers considered these findings almost unquestionable evidence of myocarditis, despite the lack of symptoms or physical signs.

They pointed out the similarity of electrocardiographic findings in this case with those commonly seen in acute rheumatic myocarditis and considered that a more widespread use of the electrocardiograph is indicated, to determine the true incidence of this complication. It is quite possible that the electrocardiographic changes noted in our series could have been of virus origin but, as previously stated, facilities to prove such a hypothesis were unavailable.

From the electrocardiographic standpoint, several of the tracings could easily be confused with changes resulting from myocardial ischemia. A few of the patients presented electrocardiographic patterns suggesting combined anterior and posterior infarction but the absence of the typical Q-wave pattern and the relatively benign clinical appearance made this diagnosis untenable.

The other conditions mentioned, as acute and chronic constrictive pericarditis, acute cor pulmonale and dissecting aneurysm, can also be quickly excluded as potential causes of these RST changes, as our patients lacked any of the typical roentgen or clinical findings characterizing these conditions.

In conclusion, it is apparent that a small, but definite, number of patients in this series of atypical pneumonia developed distinct changes in the RST segments or T-waves. A few showed disturbances in either AV or intraventricular conduction. Some of these changes were temporary, existing for a period of several weeks or months before reversal to normal. A few of the cases manifested electrocardiographic changes which were irreversible for a period in excess of four months. Strictly from the electrocardiographic standpoint, these changes were highly suggestive of pericarditis, but several investigators<sup>36, 37</sup> have shown that when pericarditis occurs, usually a diffuse subepicardial myocarditis is a concomitant finding. Some of our cases developed evidence suggesting this associated disease, such as both disturbances in conduction and inversion of the T-waves.

Obviously, the etiology of these changes was just as obscure as the etiology of the atypical pneumonic process itself. Inasmuch as none of these cases came to autopsy the full significance of these changes can not be stated with certainty.

#### CONCLUSIONS

1. Three hundred and 21 cases of atypical pneumonia were evaluated in detail.
2. The disease occurred throughout the year, but reached its greatest incidence in the winter months.
3. The onset was usually gradual, non-productive cough and fever being the outstanding symptoms.
4. Crackling râles over the involved area and some degree of pharyngitis were present in roughly two-thirds of the cases.
5. Inspiratory wheezes over the affected area furnished an important diagnostic sign early in the disease.

6. The pulse and respiratory rates were only moderately elevated in most of the cases.

7. A normal blood picture was the usual finding, but leukocytosis, either absolute or relative, did not preclude the diagnosis. Leukopenia and lymphocytosis were equally rare.

8. The sedimentation rate in most of the cases was moderately elevated and was a useful adjunct in determining the time of discharge.

9. A more accurate method of designating the site of involvement was developed. Most atypical processes originated in the hilus and extended into the dependent portion of the lungs. In nearly half of the series, the cardiophrenic angles were the chief site of involvement. The left lung was more frequently involved.

10. Treatment was chiefly symptomatic, but sulfonamides were indicated in selected cases.

11. Complications were infrequent.

12. A small number of cases (3.7 per cent) revealed changes in the RST segments, T-waves or disturbances in conduction, suggestive of pericarditis and myocarditis. Most of these changes were reversible.

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# THE MANAGEMENT OF CHRONIC ARTHRITIS AND OTHER RHEUMATIC DISEASES AMONG SOLDIERS OF THE UNITED STATES ARMY \*

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DURING the First World War about 93,000 American soldiers developed some sort of "rheumatism."<sup>1</sup> Four common rheumatic diseases—rheumatoid arthritis, rheumatic fever, osteoarthritis and muscular rheumatism—accounted for about 80 per cent of these cases (table 1).

TABLE I

Incidence of Certain Diseases \* in the United States Army  
First World War (Apr. 1, 1917 to Dec. 31, 1919)

Total of Mean Annual Strengths for the War Period = 4,128,479 Soldiers

Condition	Total Cases	Percentage	Rates Per 1000 Soldiers
Arthritis (rheumatoid and osteoarthritis)	33,613	36%	8.14
Acute Articular Rheumatism † (rheumatic fever)	24,770	27%	6.00
"Muscular Rheumatism"	12,093	13%	2.93
Gonorrheal Arthritis	7,895	9%	1.91
"Myositis"	4,135	4%	1.00
"Synovitis"	3,665	4%	.87
"Tenosynovitis"	2,671	3%	.65
"Ankylosis of Joints"	1,907	2%	.46
"Other Diseases of Joints" (non-traumatic)	1,614	2%	.39
Tuberculous Arthritis	188		.05
Gouty Arthritis	82		.02
Total	92,633	100%	22.43

\* These conditions were not fully defined in the original reference; the terms are those used in the Manual of the International List of Causes of Death, Second Revision, Paris, 1909; Washington, D. C., Government Printing Office, 1913.

† In addition to the 24,770 cases of acute articular rheumatism (rheumatic fever), there were 17,372 cases of "valvular heart disease," the great majority of which were probably rheumatic in origin.

The subsequent cost to the government of these 92,633 cases of rheumatism has never been estimated; it must have been very great. In 1931, 13 years after the war, the Veteran's Administration was paying over \$10,000,000 a year in disability compensations to about 35,000 ex-Service men with "arthritis"<sup>2</sup> and in 1943, 25 years after the war, the Veteran's

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Administration was expending annually about \$2,500,000 in pensions alone to soldiers of World War I with rheumatic heart disease.<sup>3</sup>

### NEED FOR RHEUMATISM CENTERS

During the First World War no special Rheumatism Center was officially established by the War Department. However, Major Ralph Pemberton and his associates were afforded the opportunity of studying carefully at United States General Hospital Number 9, Lakewood, New Jersey, 400 cases of chronic arthritis among soldiers.<sup>4</sup> "Although General Hospital Number 9 was never designated as a 'Center,' it functioned as one."<sup>5</sup>

During World War I the mean strength of the American Army over a period of two and three quarter years (33 months: April 1, 1917 to December 31, 1919) was 4,128,479. During every month of that period an average of 2807 soldiers developed rheumatism. If the incidence rate for "rheumatic diseases" among soldiers during that war (22.4 cases per 1000 soldiers) were maintained during this second world conflict, the War Department could expect that out of an army of 8,000,000 soldiers, there would develop within the first two and three quarter years of this war (namely, between December 1941 and August 1944, inclusive) about 180,000 cases of rheumatism, an average of about 5454 cases during every month of the war. Of these 180,000 cases, about 64,000 cases would be of chronic rheumatoid arthritis or of osteoarthritis. (Not yet available are the figures for this war.)

To prepare for such a possibility, in the fall of 1942 the Surgeon General and his Associates, with the coöperation of the American Rheumatism Association, took the first tentative steps toward the subsequent establishment of one or more Rheumatism Centers for the army if or when the need materialized.<sup>6</sup> To date the need has been such that five Rheumatism Centers have been established—two for patients with chronic rheumatic diseases and three for patients with rheumatic fever.\*

### PURPOSES OF A CENTER

The majority of soldiers who develop rheumatism need not be transferred to special Centers. Patients with transient muscular rheumatism, mild rheumatic fever without carditis, or acute traumatic or specific infectious arthritis can be handled effectively in the adjacent Station or Regional Hospital. Rheumatism Centers are designed for the care of difficult or progressive cases or for diagnostic problems.<sup>7</sup>

The chief aims of a Rheumatism Center are these:

1. Accurate diagnosis: To provide a diagnostic center where difficult cases can be studied by special methods and by medical officers with a special knowledge of rheumatic diseases.

\* Three Rheumatism Centers were recently established for the joint Services (Navy, Army, Air Force) of the Canadian Government: one at St. Thomas, Ontario opened in June 1945; others at Winnipeg and at Nanaimo, B. C., opened in April 1945.



2. Intensive treatment: To provide special facilities for the treatment of the more severe or progressive cases.

3. Prompt disposition: To accomplish as great a reduction in hospitalization-time as is consistent with adequate treatment.

4. Increased salvage: To restore to duty, if possible, more men with "cured" or "arrested disease."

5. Rehabilitation: To educate and rehabilitate for civilian life those whose disability necessitates discharge from the army.

6. Application of newer advances in treatment.

7. Appropriate clinical studies of patients while under treatment.

8. Long-range economy, an incidental, but important aim: To reduce the costly need for disability pensions and prolonged hospitalization in Veteran's Facilities.

#### THE CENTER AT THE ARMY AND NAVY GENERAL HOSPITAL

On December 17, 1943 the Surgeon General designated the Army and Navy General Hospital as the first Center for the diagnosis and treatment of rheumatic diseases.<sup>8</sup> This hospital, the Army's oldest general hospital, was chosen because of its past history and excellent facilities. Because of the adjacent hot springs this hospital has, since 1887, been a mecca for the rheumatic personnel of the army. In 1933 the old main hospital building was demolished and replaced by a large new building, and in 1943 an adjacent large hotel was acquired, renovated and connected to the main building, creating a capacity of 1342 hospital beds with an additional 383 beds for patients being reconditioned (total 1725 beds) (figure 1).

A proper knowledge of rheumatic diseases demands familiarity with all phases of general medicine. The productive record of American and European hospitals which have been devoted exclusively to the study of rheumatic diseases has often been disappointing. Rheumatism clinics and services in civilian hospitals maintain their vitality by, and derive much of their inspiration from, their close association with the other clinical and laboratory departments. Therefore, one of the chief advantages of this Rheumatism Center is its placement in a large general hospital with its varied medical and surgical specialties. Thus the rheumatic patient commands the services of specialists in many fields.

The rapid growth of the Center is shown by the daily census of the Section on Rheumatic Diseases which increased from 56 patients present on a given day in January 1944 to 704 patients actually present on a given day in October 1944. During the year 1944, 3105 "rheumatic patients" were admitted, and between January and June 1945 inclusive, 2210 additional "rheumatic patients" were admitted, a total of 5315 in 18 months.

Many of the patients have been received from various camps throughout the country, but during recent months most of the patients have come from overseas hospitals. The majority have come by boat from the South Pacific

or from the European Theater of operations, but many have come via the ambulance planes of the Air Transport Command (figure 2). The speed of evacuation of certain rheumatic patients from overseas has often been startling: some have arrived here by plane within four to six days after leaving South Pacific hospitals (e.g., within four days from Saipan to Hot Springs); others have arrived within three to seven days from England, Italy or France (e.g., from Paris to Hot Springs in three days). Such promptness in evacuating rheumatic soldiers from overseas to hospitals

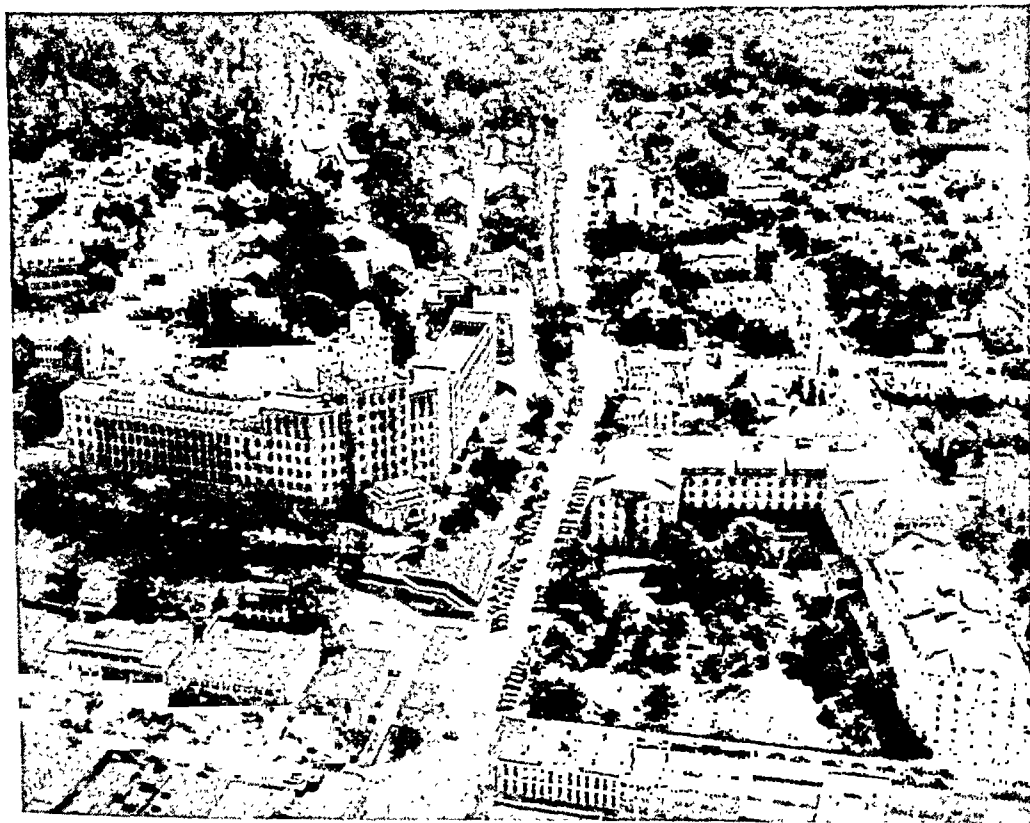


FIG. 1. The Rheumatism Center of the United States Army at the Army and Navy General Hospital; the main building (left) is now connected with the Eastman Annex (right).

equipped especially for their needs fosters a fine morale among the soldiers and their anxious relatives. A proportionate promptness in the subsequent diagnosis and disposition (consistent with adequate treatment) has done much to maintain that morale.

#### THE CENTER AT ASHBURN GENERAL HOSPITAL

Because the flow of rheumatic patients to the first Center became excessive, a second Center for chronic rheumatic diseases was established August 25, 1944 at Ashburn General Hospital, McKinney, Texas.<sup>9</sup> During its first

eight months the Section on Rheumatic Diseases at that hospital admitted about 2200 patients.<sup>10</sup>

### CENTERS FOR PATIENTS WITH RHEUMATIC FEVER

Also on August 25, 1944, the Surgeon General established three Centers for the care of soldiers with rheumatic fever<sup>9</sup>: at Birmingham General Hospital, Van Nuys, California; at Foster General Hospital, Jackson, Mississippi; at Torney General Hospital, Palm Springs, California. Within the

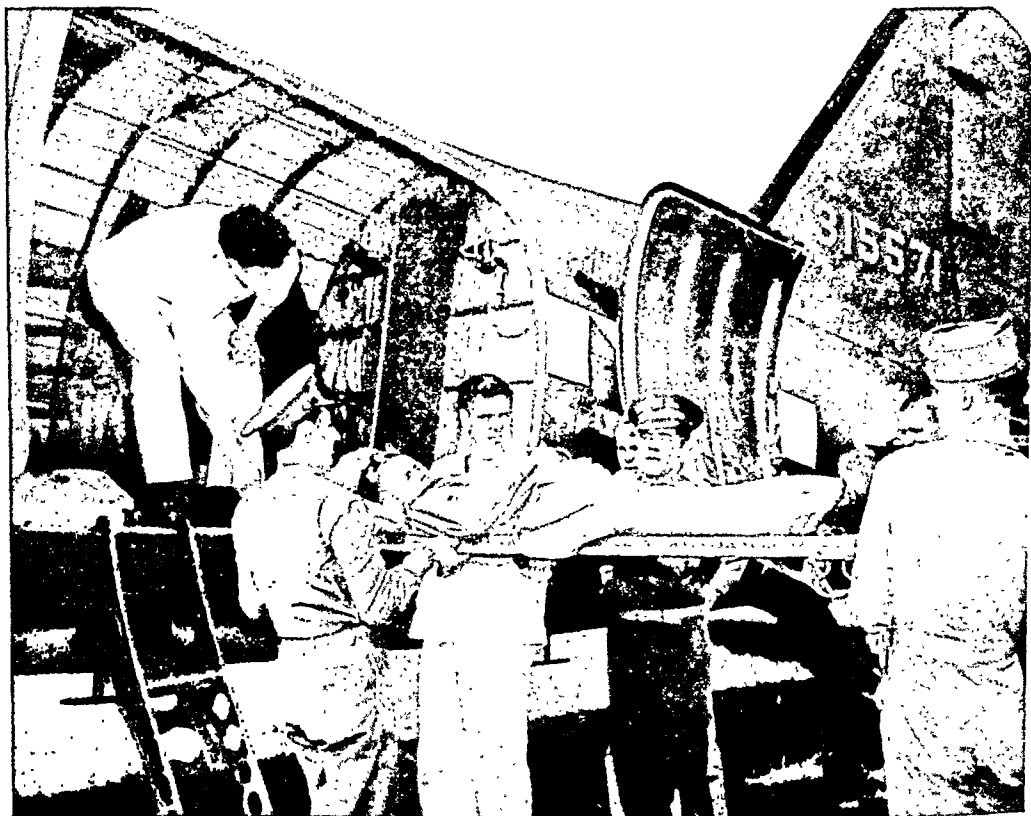


FIG. 2. Arthritic soldiers arriving at The Rheumatism Center after evacuation from overseas in the hospital planes of the Air Transport Command.

first eight months a total of about 900 patients with rheumatic fever was admitted to these three hospitals,<sup>11</sup> most of the patients having been transported thereto by air as soon as possible after the acute phase of the disease began to subside. These 900 patients with rheumatic fever comprised only a minority of the cases of rheumatic fever in the army; during 1942, 1943 and 1944 there were respectively about 1300, 7000 and 6000 cases of rheumatic fever which developed among soldiers in the United States and were recorded by the Surgeon General's office.<sup>12</sup>

The policies of the War Department regarding the diagnosis and management of rheumatic fever have been outlined.<sup>13</sup> The oral administration of

salicylates was considered generally preferable to the intravenous administration. Sulfonamide chemoprophylaxis for the prevention of recurrences was approved; the drug of choice being sulfadiazine, 0.5 to 1.0 gm. daily during the period of convalescence and reconditioning, but not of course during the acute phase of the disease.

The policies of the War Department regarding disposition of such cases are flexible, not static. In general the following patients have been separated rather promptly from Service: those with prolonged active rheumatic fever, those with frequent recurrences and those with significant cardiac involvement. But some patients in the last category who possessed unusual technical skills or other military qualifications have been retained on limited service if their cardiac lesions were well compensated. Most of the 900 patients admitted to these three Centers have been or will be returned to temporary limited duty for six months in a warm dry climate. Thereafter reexamination and final disposition will be made. To prevent psychic invalidism the War Department has advised that such temporary duty should not involve *undue* limitation of physical activity.

These three Rheumatic Fever Centers belong to the Army Service Forces. In addition, the Army Air Forces has initiated a program of rheumatic fever control in several of their southern Regional Hospitals.<sup>14, 15</sup>

#### RELATIVE INCIDENCE OF RHEUMATIC DISEASES

Because the patients sent to the Rheumatism Center at the Army and Navy General Hospital are selected, our census does not reflect the relative incidence of the rheumatic diseases in the Army as a whole. An analysis of our first 1000 cases has revealed a relative incidence as given in table 2.

TABLE II

Incidence of Various Types of Rheumatic Diseases among the First 1000 Consecutive Admissions to the Rheumatism Center, Army and Navy General Hospital

	Cases	Percentage
Rheumatoid Arthritis (including rheumatoid spondylitis).....	331	33.1%
"Psychogenic Rheumatism".....	200	20.0%
Osteoarthritis (primary and posttraumatic).....	136	13.6%
Fibrositis (intramuscular and/or periarticular; bursitis, supraspinatus tendinitis, etc.).....	134	13.4%
Rheumatic Fever.....	22	2.2%
Gonorrheal Arthritis.....	13	1.3%
Gout.....	10	1.0%
Miscellaneous Conditions (Listed in the order of relative frequency):		
Sciatica, backache due to ruptured intervertebral disks and other causes, internal derangements of knees, nonspecific monarthritis, traumatic arthritis and synovitis, tuberculous arthritis, psoriatic arthritis, palindromic rheumatism, joint tumors and rare forms of joint disease.....	113	11.3%
Unclassified Diseases of Joints and Related Structures.....	41	4.1%
	1000	100 %

A more detailed survey is being prepared for a later report. These figures may be compared to the incidence of rheumatic diseases as seen in a General Hospital which is not a Rheumatism Center.<sup>16, 17</sup>

Here, as in all rheumatism clinics, rheumatoid arthritis presented the main problem; it affected one third of all patients admitted. About one fifth of the patients admitted as "rheumatic" had no significant organic skeletal disease. They suffered from psychoneurosis manifested by musculoskeletal symptoms, a condition called by some "psychogenic rheumatism,"<sup>17</sup> by others "psychoneurotic rheumatism"<sup>18</sup> or "psychosomatic rheumatism."<sup>19</sup> This condition will be discussed later herein. Because of the relative youth of soldiers, the incidence of gout and gouty arthritis has been low, the relative incidence being 1 per cent as compared to a relative incidence of 4 or 5 per cent frequently seen in civilian rheumatism clinics. Thanks to modern chemotherapy the total and relative incidence of gonorrheal arthritis has been low.

About one third of our cases of rheumatoid arthritis have been rheumatoid spondylitis, a relative incidence surprisingly high and in notable contrast with experiences in civilian practice. At this Center, for many months we have had at any given time from 70 to 100 cases of rheumatoid spondylitis. The relative frequency of such cases among soldiers probably arises from three factors: (1) Rheumatoid spondylitis affects males much oftener than females, and especially affects young males of military age (18 to 30 years). (2) The early symptoms of the disease, such as vague intermittent low back pain, are difficult to evaluate and an early diagnosis is often not made. Many such early cases in young men have not been recognized until after their induction into the Army. (3) The strenuous physical exertions of Army life and training soon aggravate the symptoms and bring to light these early, previously undiagnosed, cases.

The figures on the relative incidence of rheumatic diseases as seen at our Center are, with a few exceptions, in close agreement with those from the Center at Ashburn General Hospital. Through the courtesy of the Commanding Officer and Staff of that hospital we are permitted to report the relative incidence of "rheumatic diseases" among their first 800 completed cases<sup>10</sup> (table 3).

TABLE III  
Incidence of "Rheumatic Diseases" at The Rheumatism Center

Ashburn General Hospital First 800 Completed Cases	
Rheumatoid Arthritis.....	38.3 per cent
Osteoarthritis.....	26.7 per cent
"Psychogenic Rheumatism".....	16.1 per cent
Postural Backache.....	2.6 per cent
Internal Derangement.....	1.8 per cent
Extra-articular Disease (e.g., bursitis) exclusive of fibrositis.....	1.6 per cent
Specific Infectious Arthritis exclusive of tuberculous arthritis.....	1.4 per cent
Protruded Intervertebral Disk.....	1.3 per cent
Tumors.....	0.7 per cent
Fibrositis.....	0.6 per cent
Gouty Arthritis.....	0.6 per cent
Tuberculous Arthritis.....	0.2 per cent
Miscellaneous.....	8.1 per cent

100 per cent

Thus at the two Centers the relative incidences were: rheumatoid arthritis 33 and 38 per cent, "psychogenic rheumatism" 20 and 16 per cent, specific infectious arthritis (including gonorrheal and tuberculous arthritis) 1.9 and 1.6 per cent, and gouty arthritis 1.0 and 0.6 per cent.

### PROBLEM OF DIFFERENTIAL DIAGNOSIS

So relatively inadequate was the general knowledge of the arthritides 25 years ago that a diagnosis of "acute arthritis" or of "chronic arthritis," made without further qualification, was then excusable. Thus the articular and muscular conditions encountered in the First World War were often not clearly defined (table 1). Today an unqualified diagnosis of "acute arthritis" or of "chronic arthritis" is considered inadequate except in rare instances. Although there are many types of acute and chronic arthritis, the rheumatologist and the interested internist should be able usually to subdivide them and state *what kind* of "chronic arthritis" is present. This is a matter of considerable importance in treatment, but especially is it important for a proper estimate regarding prognosis and military disposition.

An analysis of the transfer diagnoses, those with which the patients arrived at the Center, has revealed scores of patients sent here for "arthritis" who had no arthritis at all. Many patients presumably with "osteoarthritis" actually had rheumatoid arthritis, and vice versa. Few of the cases of gout had been correctly diagnosed. A great many of the patients with "muscular rheumatism" actually had, not myositis or fibrositis, but "psychogenic rheumatism"—psychoneurosis manifested by musculoskeletal complaints. Such errors in diagnosis are no particular reflection on medical officers. They merely reflect the diagnostic level of the medical profession as a whole in matters rheumatologic, and exhibit once more the need of physicians in general for a wider and more critical knowledge of fundamentals in the diagnosis of diseases of joints.

### DIFFERENTIATION OF GONORRHEAL ARTHRITIS FROM RHEUMATOID ARTHRITIS PRECIPITATED OR AGGRAVATED BY GONORRHEA

It is not sufficiently understood that rheumatoid arthritis can be precipitated by a gonorrheal infection just as it can be precipitated by tonsillitis, influenza or some other acute infection. Also a mild, intermittent or quiescent rheumatoid arthritis can be aggravated by acute genital gonorrhea. Such cases have sometimes been called "post-gonorrheal rheumatoid arthritis" but this condition does *not* represent chronic rheumatoid arthritis engrafted on, or evolving from, a subsiding acute gonorrheal arthritis; it represents simply rheumatoid arthritis precipitated or aggravated by acute genital (not articular) gonorrhea. This entity is not new to the experienced rheumatologist. It is regularly encountered in civilian practice, and in 1 per cent of Pemberton's cases of chronic arthritis among soldiers in the last

World War the arthritis began in close relationship with the onset of gonorrhea.<sup>4</sup>

Proved gonorrheal arthritis among American soldiers in this war appears to be rather rare. In this Rheumatism Center we have seen many more cases of rheumatoid arthritis precipitated or aggravated by gonorrhea than of gonorrheal arthritis. Most of the former cases have been erroneously labelled gonorrheal arthritis, treated as such unsuccessfully by sulfonamides or penicillin or by fever therapy, and transferred to our Center labelled "gonorrheal arthritis resistant to penicillin and/or sulfonamides." In our experience, most cases of so-called "gonorrheal arthritis resistant to chemotherapy" have turned out to be cases of rheumatoid arthritis as shown by their subsequent course, therapeutic tests and, in some cases, articular biopsies.<sup>20</sup> This matter will be the subject of a later report.

#### PSYCHONEUROSIS MANIFESTED BY MUSCULOSKELETAL SYMPTOMS: "PSYCHOGENIC RHEUMATISM"

Physicians in general are familiar with psychoneurosis as it may affect the gastrointestinal tract (functional dyspepsia, neurasthenia gastrica, irritable colon, anorexia nervosa, etc.) or the cardiovascular system (cardiac neurosis, soldier's heart, neurocirculatory asthenia). Physicians are not so familiar with psychoneurosis as it affects the locomotor system.

"Psychogenic rheumatism," the musculoskeletal expression of functional disorders, tension states or psychoneurosis, is one of the commonest causes of generalized or localized aches and pains in muscles or joints or both, either in civilian or military life. It may exist alone or may occur as a functional overlay of some rheumatic disease such as fibrositis or rheumatoid arthritis. The designation "psychoneurosis manifested by musculoskeletal complaints" is more proper than the terms "psychogenic rheumatism" or "psychosomatic rheumatism." But the term "psychogenic rheumatism" persists in token of its compactness and handiness; if its limitations are understood, it can be a useful label.

Many inadequate, unadaptive soldiers unconsciously make "flight into illness" via musculoskeletal complaints which they, and some physicians also, erroneously call "rheumatism" or "arthritis." These patients have many symptoms but no objective, constitutional, roentgenographic or biochemical manifestations of disease. Actually these patients have no real "rheumatism," no true synovitis, arthritis or organic muscular lesion, or if some minor musculoskeletal disease does coexist it is insufficient to account for the severity of the disability. The clinical pattern is not that of organic rheumatic disease. Typical functional complaints referable to other systems often may be elicited. The degree of psychoneurosis present may vary from a mild anxiety tension state to a major conversion hysteria; camptocormia (hysterical bent back), bizarre gaits, peculiar articular postures or hysterical flexed fingers are not uncommon.

It will be noted that about 20 per cent of our patients and about 16 per cent of those admitted to the Center at Ashburn General Hospital had no significant organic rheumatic disease, at least by the time they reached the Centers (tables 2 and 3). They either had "psychogenic rheumatism" alone, having had no organic "rheumatic disease" at all, or they had a dominating "psychogenic rheumatism" which completely overshadowed an initial and still underlying mild fibrositis or arthritis, or which had completely replaced a previous rheumatic disease (e.g., fibrositis or rheumatic fever), no longer active.

The prompt recognition of "psychogenic rheumatism" is of great importance in the Army to prevent the continuation of the disorder to the point of irreversibility, to prevent unnecessary and unjustified discharge of men on life-time pensions for non-existent "arthritis" or "fibrositis," and, above all, in order to institute the proper methods for the physical and psychic rehabilitation of these unfortunate and generally misunderstood patients.

#### DIFFERENTIATION OF "PSYCHOGENIC RHEUMATISM" FROM FIBROSITIS

Primary fibrositis is the chief rheumatic disease from which "psychogenic rheumatism" must be differentiated. In general, primary fibrositis puts its victims at the mercy of changes in *external* environment: thus weather, heat, cold, humidity, rest, exercise, etc., characteristically influence most of them for better or worse. On the other hand "psychogenic rheumatism" generally puts its victims at the mercy of changes in *internal* environment: thus their symptoms may vary with mood or psyche, pleasure, excitement, mental distraction, worry or fatigue.

TABLE IV

Tabular Differentiation between Fibrositis and "Psychogenic Rheumatism"; Generalities

	Fibrositis, primary type	"Psychogenic Rheumatism"
General attitude	Coöperative, earnest, "objective"	Tense, anxious, "subjective," defensive, antagonistic
Chief complaint	"Joints hurt and feel stiff"	"Can't quite describe it, doctor. It's like . . ."
Chief symptoms	Aching, soreness, stiffness, fatigue	Burning, tightness, weakness, numbness, tingling, queer or tired sensations
Time of day when symptoms are worse	Morning and/or late afternoon	Inconstant—often continuous day and night
Aggravation or amelioration dependent on:	External or physical environment	Internal or mental environment
Effect of mental preoccupation: (theatre, movie, bridge, etc.)	No definite relief, symptoms intrude	Often marked relief but perhaps "pays for it afterwards"



TABLE IV.—*Continued*

	Fibrositis, primary type	"Psychogenic Rheumatism"
Symptom Analysis		
1. Pain:		
Amount	+ to ++	+ to +++
Constancy	Varies in intensity during day: worse in morning, better at noon, often worse again later in day	Tendency to be constant, "bad all the time"
Duration	Hours or days Remissions, exacerbations	Momentary or constant, "no different," getting worse.
Location	Anatomical	Often not anatomical
Migration	May not migrate; if so migrates in anatomical fashion	Bizarre, hemalgia, etc.; may follow no anatomic pattern
2. Stiffness	Worse after much rest (jelling). More marked in early morning. Better after mild exercise.	Minimal or not present. Jelling not characteristic.
3. Fatigue	A.M. on waking: 0 to + P.M. ++ "Disability causes fatigue"	Early A.M. + to +++ May be constant "Fatigue causes disability"
Effect of rest	After prolonged rest—worse (jelling)	Improvement or no effect
Effect of exercise	Better "limbers up"	Worse during and after
Effect of applied heat	Temporary relief—hours	Variable—often worse
Effect of weather	Worse when cold and damp. "Weather prophet."	Variable
Effect of therapy:		
In general	Temporary relief	"Nothing helps me, doctor"
Patient's attitude	Admits relief	Defies finding a cure
Aspirin	Temporary relief—hours	Usually no relief (aspirin futility), or "never tried it" (aspirin inutility)
Physical therapy	Temporary relief	Variable—often worse
Response to examination:	Coöperative; tenderness consistent	Fearful, resistant; "touch me not" reaction
"Extras" (associated functional complaints)	0 to +	+ to ++++ Bizarre limps and postures, headaches, globus hys- tericus, sighing respira- tions, precordial pains, insomnia, nervousness, tremor, etc.

Space does not permit the inclusion here of more than a tabular differentiation in general terms (table 4). The differentiation depends, of course, not on any one feature but on a combination of features. When a case of one or the other disorder is relatively "pure," differentiation is readily made. Differentiation and a correct assay of the problem are especially difficult when a mild fibrositis coexists with a marked functional overlay. Nevertheless this differentiation has been very useful to us.

## TREATMENT

The comprehensive schemes of treatment, used at this Center, for the various rheumatic diseases are those approved by the American Rheumatism Association <sup>21</sup> and used by the leading rheumatologists of the country. This Center does have unusual facilities for physical therapy and hydrotherapy; these facilities are used properly but without undue emphasis and certainly not to the exclusion of any other useful measure.

*Group lectures:* Rheumatic victims are, in general, docile, patient and well-behaved. Of their physicians they ask surprisingly little; in lieu of the elusive "rapid-cure," they ask only for a diagnosis and a decent understanding of what they are up against, what they can do to help themselves, and what they should not do lest they make themselves worse. They will abandon the physician who brushes them off with an incomplete diagnosis or a fancy diagnosis in medical terms and "a few well chosen words." To answer their need, we have instituted here a regular rotating series of group consultations or "lectures on rheumatism" given in laymen's language. Of the 12 different lectures, two or three are on general topics for all patients; others are given to the appropriate groups of (generally 25 to 100) patients with a particular disease. One group of patients is usually not admitted to the specific lectures designed for another group. Especially are patients with "psychogenic rheumatism" not permitted to attend the lectures for patients with rheumatoid arthritis or fibrositis lest misinterpretations arise. Instead, those with "psychogenic rheumatism" hear special talks designed for their particular needs and given jointly by a rheumatologist and psychiatrist.

The lectures are on the following subjects: (1) The meaning of rheumatism and arthritis; (2) facts, fads and false concepts about rheumatism; (3) fibrositis—its meaning and management; (4) rheumatoid arthritis and its management; (5) rheumatoid spondylitis and its management; (6) facts about osteoarthritis; (7) gout and gouty arthritis; (8) shoulder disabilities and their management; (9) body mechanics in relation to disability of joints; (10) home physical therapy (motion picture and demonstration); (11) emotional tension and its relation to "rheumatism"; (12) the management of rheumatic fever.

These group consultations are not a substitute for, but supplemental to, individualized consultations. They are designed to project beyond the period of Army hospitalization and into the patient's home at least some of the benefits he may derive from the more formal treatments here. They also serve as an introduction to the advice which each patient will later receive from his home physician. The lectures have been well received, and incidentally, have been a great time-saver for the busy medical officer. After each lecture the patients are encouraged to ask questions on points that bother them, no matter how trivial they may seem; any question about something not understood is a valid question. The lectures also improve morale:

seeing that he is not alone in his problem and that others are worse than he, the patient takes courage.

*Rheumatoid arthritis:* Our treatment for this disease is quite standard and includes the removal of obviously infected foci, the use of highly nutritious diets (but there is no "anti-rheumatism vitamin" or specific diet), foreign protein therapy in selected cases, simple analgesics, physical therapy, occupational therapy, orthopedic measures to prevent or correct deformities, gold salts carefully administered to selected patients whose rheumatoid arthritis is progressive in spite of more conservative measures, and roentgen therapy for certain cases of rheumatoid spondylitis. We found penicillin to be ineffective.<sup>22</sup>

*Psychogenic rheumatism:* The treatment of psychogenic rheumatism has been an interesting but difficult problem, second here in importance only to that of the treatment of rheumatoid arthritis. Our pleasure at being able to reassure soldiers with psychogenic rheumatism that they do not have arthritis or muscular rheumatism and that they need not fear the presence of a crippling disease is tempered by the difficulty of helping them to develop insight and to accept their diagnosis, at least to the point of submitting whole-heartedly to a trial of psychotherapeutic reconditioning. In these cases the latter is of much greater value than physical reconditioning; physical reconditioning used alone in these cases accomplishes little or nothing.

Patients with psychogenic rheumatism are not generally given formal courses of physical therapy or other treatments used for "organic rheumatism" except as diagnostic or therapeutic tests, because such treatments often tend to fix more firmly in their consciousness the belief that they have organic disease.

#### THE DISPOSITION OF RHEUMATIC SOLDIERS

Nothing could destroy a soldier's potentialities for salvage (his morale, his will to recover and to serve) more readily than the atmosphere of a "chronic hospital," a "rheumatic old soldier's home." The rheumatic soldier should not be kept in a state of prolonged uncertainty as to whether he will probably be returned to duty (limited duty, if necessary) or whether he will be discharged from the Army. Whatever his future is to be, it should be, relatively speaking, an immediate future, not a vague distant future. No hasty dispositions should be made, but in most cases it does not take long to determine the probable disposition required for a given rheumatic disease or the future military potentialities of a given rheumatic soldier. Furthermore, "right or wrong," a disposition should be made fairly promptly, unless prolonged definitive treatment is indicated; otherwise the rheumatic soldier may develop the hospital habit, the outlook of the dependent chronic invalid or pensioner. If hospitalized too long, a salvable patient with a mild form of rheumatism may, even though he was originally well oriented, develop some form of hospital-engendered psychoneurosis or

fixation of illness, and the functional overlay may become more difficult to treat than the original organic disease upon which it became superimposed.

To combat these possibilities, each patient on arrival is told that his stay is decidedly not indefinite, that his period of hospitalization will follow a rather definite and progressive, though elastic, schedule: a few days for a thorough initial physical survey, then a period of intensive treatment (generally about three to eight weeks, longer in selected cases), after which it will be decided whether he can be "reconditioned" for further military service or should be "rehabilitated" for civilian life.

*Reconditioning:* Getting a convalescent soldier physically and mentally prepared to return to military duty is spoken of as "reconditioning."<sup>23</sup> The salvable rheumatic soldier is "reconditioned," first in the hospital by the medical program noted above, then by a supplemental period of two or more weeks during which time he lives in a convalescent barracks and undergoes daily a program of physical activity carefully measured to his abilities. Some patients recovering from a transient rheumatic disease can participate in a fairly strenuous program; for other patients who at best can only be expected to return to limited service, the reconditioning program is less strenuous; in every instance an attempt is made to apply the program as an individual prescription.

*Rehabilitation:* If a soldier's rheumatism precludes the possibility of his return to duty within a reasonable period of time, if his disease is essentially progressive and disabling, the soldier will be made ready for discharge to civilian life and for subsequent follow-up treatments by his civilian physician or, if necessary, by a Veteran's Facility. To such a soldier, as to the one who can return to duty, the Army acknowledges an equal obligation: getting him prepared mentally and physically to return to a useful civilian life, despite his rheumatic disability, is spoken of as "rehabilitation."

After his discharge from the Army, the arthritic patient may have to modify the patterns of his life somewhat, so as to avoid factors known to be aggravating to his disease, but he must not alter his life to the point of engendering defeatism. The educational program mentioned heretofore is one of our chief weapons against the dangers of a wheel chair—or crutch-psychology. The discharged arthritic patient must still regard himself as a vital unit of his community. We therefore attempt to teach him how to live with his disease, not for it. As long as possible, the treatment of his rheumatism should be merely an avocation, not his vocation. If prematurely or needlessly he makes a vocation of his disease, he has taken a long step toward the sterile existence of the pensioner's rocking chair.

*Policies:* Each of the rheumatic diseases poses its own problem in disposition.

For patients recovering from acute rheumatic fever the disposition must take into account the presence or absence of rheumatic carditis or the likelihood of its early development. The need for manpower has been such that blanket discharges for rheumatic fever could not be entertained. Disposi-

tions have been individualized.<sup>13</sup> The general policy in force at the Rheumatic Fever Centers has been mentioned.

Most patients with rheumatoid arthritis, certainly those with progressive disease, should be discharged. However, we have attempted to salvage the mildly affected patients whenever possible; otherwise we cannot learn to what extent salvage is feasible or to what extent the Army can utilize the soldier with a clear brain and a stout heart, but with slightly rheumatic joints.

The disposition of patients with "psychogenic rheumatism" requires individualized consideration. Many soldiers affected with psychoneurosis of mild or moderate degree can still render effective service. But we are ordered to conserve, not men, but manpower. When, despite conscientious treatment, "psychogenic rheumatism" persists to the extent that its victim no longer represents a unit of manpower, then he is recommended for discharge, because a man without power is a drag on the Army.

#### STATISTICS ON DISPOSITION

For this report we have summarized the dispositions made on 1300 cases, not chosen serially but selected only so as to include a representative number of cases of each of the commoner rheumatic diseases (table 5). Of

TABLE V  
Disposition of 1300 Soldiers with Rheumatic Disease  
The Rheumatism Center, Army and Navy General Hospital

Condition	Patients	Returned to Duty (full or limited duty)		Separated from Service by Medical Discharge or Retirement	
		Patients	Per cent	Patients	Per cent
Rheumatoid Arthritis, including Rheumatoid Spondylitis	500	76	15.2	424	84.8
"Psychogenic Rheumatism"	200	128	64.0	72	36.0
Fibrositis, primary	150	123	82.0	27	18.0
Osteoarthritis	100	38	38.0	62	62.0
Rheumatic Fever	50	39	78.0	11	22.0
Gonorrheal Arthritis	20	13	65.0	7	35.0
Gout	10	1	10.0	9	90.0
Miscellaneous and Unclassified Cases of Arthritis and "Rheumatism"	270	171	63.4	99	36.6
Total	1300	589 patients = 45.3%		711 patients = 54.7%	

the 1300 patients, 589 or 45.3 per cent were returned to duty of some kind, to full duty or to temporary or permanent limited duty; 711 or 54.7 per cent were discharged (enlisted men) or retired (officers) from service. Thus about half of the patients were returned for a further trial of duty. In contemplating these preliminary results one must keep in mind the fact that military duty, even limited duty, is pretty strenuous business, unsuited for

those who cannot work regularly at least eight hours a day. The concessions that can be made to the rheumatic soldier are limited.

A follow-up study is being made of both groups: of the retained group to note to what extent our attempts at salvage were successful; of the discharged group to note the further course of the disease when the patients were freed from the physical and psychic stresses of Army life.

It will be noted that most of the patients with primary fibrositis, "psycho-genic rheumatism," rheumatic fever or gonorrheal arthritis were returned to duty, whereas the majority of those with rheumatoid arthritis, osteoarthritis or gout were separated from service. Many of our osteoarthritic patients were elderly commissioned or non-commissioned officers of long services in the Army. In our opinion most gouty patients are not suitable for Army life, considering the difficulties of following a medicinal and dietary regime and the likelihood of encountering provocative physical trauma. Frequent recurrences of acute gouty arthritis make such persons of limited or doubtful military value.

#### CLINICAL INVESTIGATION

"It is hoped to make this hospital a source of extensive knowledge on arthritis for the whole medical profession. Studies will be carried on in the use of special drugs, such as sulfonamides and penicillin, in the treatment of arthritis": so read the War Department's announcement of the establishment of the first Rheumatism Center.<sup>7</sup> Thus the Army acknowledged an obligation to the arthritic soldier, not merely as an individual, but as a representative of all his kind. Thus the medical officers serving at the five Rheumatism Centers are encouraged to improve our clinical knowledge of the rheumatic diseases, to improve, if possible, our methods of treatment, and to present clearly the results to the medical profession. In an effort to fulfill this obligation a number of clinical investigations are being carried out at each of the five Centers. Although quite young, the two Centers for chronic rheumatic diseases are already, so far as we know, the largest Rheumatism Centers in the world. As treatment Centers and carefully supervised schools of rheumatology, they are providing a unique opportunity which should benefit mutually both the rheumatic soldier and his medical officer.

#### SUMMARY

"While arthritis does not account for a large percentage of illnesses in the United States Army, it has been found to be one of the most disabling": so the War Department has stated.<sup>7</sup> During the First World War about 93,000 American soldiers developed some type of "rheumatism," an incidence rate of 22.4 per 1000 soldiers. The incidence of rheumatic diseases among soldiers in the Second World War has been such that the Surgeon General

has established five Rheumatism Centers for selected cases: two for chronic rheumatic diseases, three for rheumatic fever.

The management of rheumatic soldiers at one of the Centers has been outlined. Rheumatoid arthritis, psychoneurosis manifested by musculoskeletal symptoms ("psychogenic rheumatism"), primary fibrositis and osteoarthritis were the conditions most often encountered. The high relative frequency of rheumatoid spondylitis and of "psychogenic rheumatism" were of special interest. Gonorrheal arthritis among soldiers appears to be relatively uncommon. More often seen were cases of rheumatoid arthritis precipitated or aggravated by acute genital (not articular) gonorrhea. It is believed that many, if not most, cases of so-called gonorrheal arthritis resistant to sulfonamides or penicillin or both are in reality cases of rheumatoid arthritis precipitated or aggravated by, or coincident with an otherwise unrelated genital gonorrhea.

Psychoneurosis manifested by musculoskeletal symptoms, "psychogenic rheumatism," has presented a common and difficult problem and affected 15 to 20 per cent of the soldiers, presumably "rheumatic," admitted to the two Centers for chronic rheumatism. The recognition of "psychogenic rheumatism" is of importance in military life in order to initiate effective treatment promptly and to prevent unnecessary discharges and pensions for non-existent "arthritis" or "muscular rheumatism." Psychogenic rheumatism must be differentiated especially from primary fibrositis (muscular or capsular rheumatism). In general fibrositis puts its victims at the mercy of changes in external environment (weather, heat, cold, humidity, rest, exercise) whereas "psychogenic rheumatism" tends to put its victims at the mercy of changes in internal environment, symptoms being altered for better or worse by changes of mood or psyche, by pleasure, excitement, mental distractions, worry, or fatigue. The clinical differentiation has been outlined briefly.

Of 1300 "rheumatic patients" disposed of at one of the Centers for chronic rheumatism, 45 per cent were returned to some type of military duty; 55 per cent were separated from Service.

The five Rheumatism Centers are providing an unusual opportunity to give the rheumatic soldier the best available study and treatment and to advance the knowledge of rheumatic diseases.

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# RHEUMATIC HEART DISEASE IN NEW GUINEA: INCLUDING A CARDIOVASCULAR SURVEY OF 200 NATIVE PAPUANS \*

By HAROLD D. LEVINE, Lt. Col., A.U.S., F.A.C.P.

IN October 1944 Major A. M. Harvey of Baltimore showed the writer a case of rheumatic heart disease with mitral and aortic stenosis and insufficiency in a native with acute cardiac decompensation at the Native Hospital conducted by Angau (Australia-New Guinea Administrative Unit) at Lae, Mandated Territory of New Guinea. This patient died a few weeks later but permission for a postmortem examination was not obtained. In view of the prevalent belief that rheumatic fever and rheumatic heart disease are only exceptionally encountered in the tropics, this case was considered a medical rarity. However, in January 1945, when the author had the privilege of accompanying a Malaria Research Unit of the United States Army in an investigation of natives along the Papuan Gulf, the opportunity was taken to investigate the frequency among them of rheumatic heart disease and any other abnormalities of the cardiovascular system.

For this purpose a group of 200 native Papuans of random age and sex distribution living in the villages of Uritai and Seapiapi was examined. The location of these villages is shown on the map (figure 1). The examination of these individuals included palpation of the brachial, radial, temporal and dorsalis pedis arteries, ophthalmoscopic examination, careful examination of the heart, lungs and abdomen, and determination of the blood pressure with an anaeroid sphygmomanometer. Hemoglobin estimations were made by the Tahlqvist method in all individuals with murmurs. Although the inaccuracy of this method is appreciated it is felt that from it a qualitative statement is warranted that the subject does or does not have anemia. Electrocardiograms and roentgenograms of the chest were not feasible. In view of the fact that the determination of the left border of cardiac dullness by percussion would not be universally acceptable as evidence of heart size, a statement regarding heart size was not made unless the position of the maximum apical impulse of the heart was felt. In view of the lack of evidence of cardiac displacement from physical examination, location of the apex impulse to the left of the midclavicular line was arbitrarily accepted as evidence of cardiac enlargement. Murmurs were graded on the basis of one to six, grade one being the faintest murmur audible on careful auscultation and grade six, one which may be heard with the naked ear at some distance from the chest.<sup>1</sup>

Accurate records were available on the ages of all individuals in the younger age group, but the age given for the older members of the com-

\* Received for publication September 1, 1945.

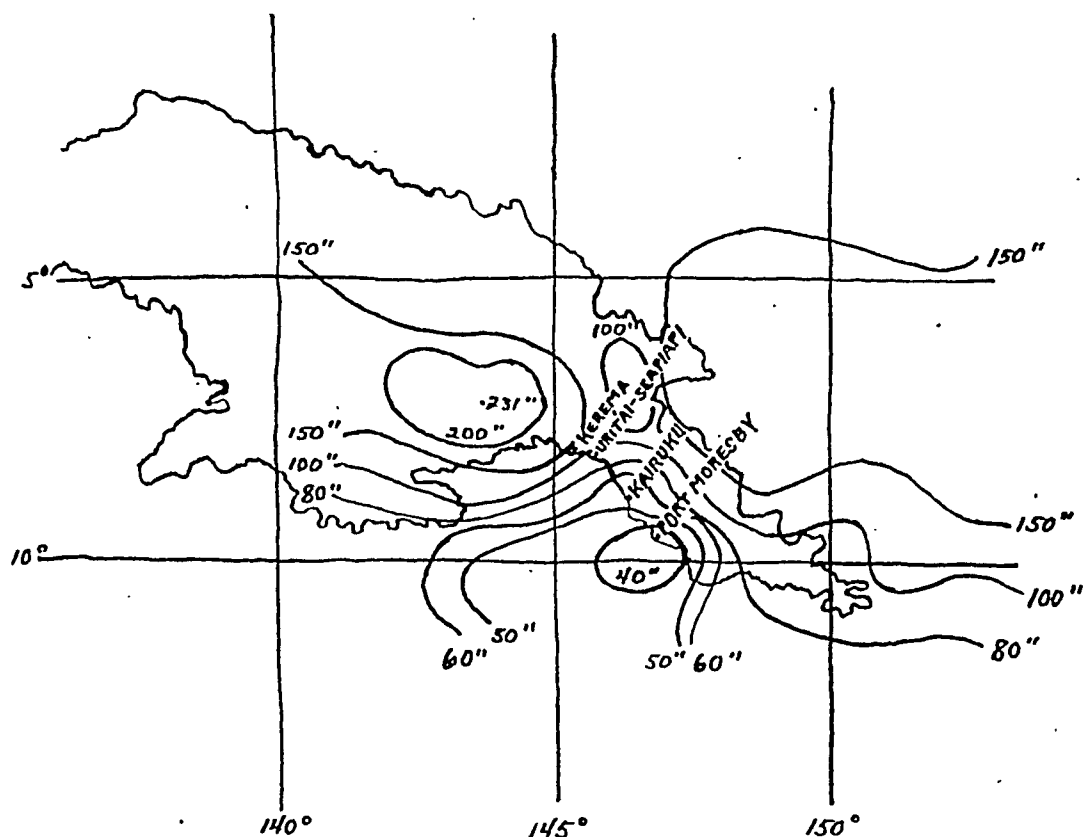


FIG. 1. Isohyetal map of eastern New Guinea showing the location of the villages studied.

munity is only approximately correct. The scarcity of elderly individuals is at once apparent in chart 1. Only 20 people (10 per cent) were more

#### CHART I

##### Age Distribution of Individuals with Cardiac Murmurs, Cardiac Enlargement and Peripheral Arteriosclerosis

Age Group	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-50	51+	Total
Number of Individuals	23	40	50	15	16	9	9	18	13	7	200
Murmurs Due to Rheumatic Heart Disease	0	2	0	0	0	0	0	0	0	0	2
Murmurs Due to Anemia	4	7	8*	3	4	1	0	1	0	1	29
Unexplained Systolic Murmurs	0	0	3	1†	0	0	0	0	0	0	4
Cardiac Enlargement Due to Anemia	2	0	2	0	0	0	0	0	0	0	4
Unexplained Cardiac Enlargement	0	0	0	0	1	0	0	1‡	1‡	0	3
Peripheral Arteriosclerosis	0	0	1	2	4	3	1	6	7	5	29
Retinal Arteriosclerosis	0	0	0	0	0	0	0	0	0	0	0

\* The murmur in one of these individuals was also explicable on the basis of fever, tachycardia and active dermatitis.

† "Possible heart disease": other members of this patient's family also had murmurs.

‡ Each of these individuals had peripheral arteriosclerosis.

than 40 years of age. From a superficial examination one would say that the population apparently ages rapidly. A man or woman of 30 or 35 will usually already have developed some of the stigmata of senility, loss of elasticity of the skin, arcus senilis or thickening, tortuosity or prominence of the visible arteries. Random notes taken at the time of this study state "this man of 30 looks 50," "a wizened old fellow of 35," or "a grizzled matron of 39 with peripheral sclerosis and arcus senilis." There were 108 females and 92 males in the sample studied.

*The Detection of Cardiac Murmurs.* In 165 individuals no murmurs

CHART II

Auscultatory and Palpatory Findings and Hemoglobin Values in  
Individuals with Heart Murmurs

No.	Age	Sex	Murmur		PMI cm.*	MCL cm.*	HB % (T)	Splenic Index	Interpretation of Murmur	Interpre- tation of Enlargement
			Grade	Location						
1	10	F	1 systolic mid-diastolic rumble	Apex Apex	—	—	50	3	Mitral stenosis. Rheumatic heart disease	—
2	9	M	2 systolic 2 systolic mid-diastolic rumble	Apex 2nd & 3rd lis Apex	8.5	6.3	70	3	Mitral stenosis and insufficiency. Rheumatic heart disease	Same
3	12	F	3 systolic and thrill 2 systolic	Base trans. to neck Apex	10.0	6.5	50	3	Unexplained. ?Aortic stenosis	Unexplained
4†	14	M	2 systolic 1 systolic	Apex lsm	8.0	7.2	70	0	Unexplained. ?Mitral insuffi- ciency. Migratory polyarthritis at 7	Same
5	16	F	2 systolic 2 systolic	Base Apex	—	—	70	0	"Possible heart disease"	—
6†	13	M	1+ systolic (musical)	Apex	—	—	80	1	Unexplained	—
7	15	M	2+ systolic	Apex	—	—	60	2	Anemia	—
8	7	F	2 systolic (musical)	Apex	—	—	60	3	Anemia	—
9‡	14	F	2 systolic 1+ systolic	Apex 2nd lis	9.0	7.5	60	3	Anemia	Anemia
10	30	F	2 systolic	Apex	8.0	5.8	50	3	Anemia	Anemia
11‡	21	M	2 systolic	Apex	10.0	8.0	70	2	?Anemia	Anemia
12	22	M	2 systolic	Apex	—	—	70	0	?Anemia	—
13	11	F	1 systolic 2 systolic S <sub>1</sub> snapping	Apex 1st & 2nd lis	—	—	55	2	Anemia	—
14	3	M	2 systolic	3rd & 4th lis	—	—	60	2	Anemia	—
15	14	F	2 systolic	2nd lis	—	—	60	2	Anemia	—

\* A hyphen in these columns indicates either that the apex impulse was not felt, or, if felt, was not located to the left of the midclavicular line.

† Numbers 4, 6 and 35 are brothers.

‡ Numbers 9, 11, 16 and 40 are siblings. A third sister had a normal heart without murmurs.

lsm = left sternal margin. lis = left interspace.

PMI = Position of maximal cardiac impulse to the left of the midsternal line.

MCL = Distance from midsternal line to midclavicular line.

CHART II—Continued

No.	Age	Sex	Murmur		PMI cm.*	MCL cm.*	HB % (T)	Splenic Index	Interpretation of Murmur	Interpreta- tion of Enlargement
			Grade	Location						
16†	16	F	1 systolic 2 systolic	Apex 2nd lis	9.5	7.6	60	2	Anemia	Anemia
17	20	F	1 systolic 1 systolic	Apex Base	—	—	50	2	Anemia	—
18	6	F	1 systolic	Apex	—	—	50	3	Anemia	—
19	24	M	1 systolic	Apex	—	—	50	2	Anemia	—
20	14	M	1 systolic	Apex	—	—	50	2	Anemia	—
21	25	M	1 systolic	Apex	8.5	7.3	60	0	Anemia	Anemia
22	36	M	1 systolic	Apex	8.5	8.0	60	0	Anemia	Anemia
23	5	M	1 systolic	lsm	—	—	50	2	Anemia	Anemia
24	10	M	1 systolic	lsm	—	—	50	2	Anemia	—
25	13	F	1 systolic	lsm	—	—	50	3	Anemia, fever, tachycardia and dermatitis	—
26	17	F	1+ systolic	3rd & 4th lis	—	—	50	3	Anemia	—
27	8	M	1+ systolic (musical)	3rd lis	—	—	50	2	Anemia	—
28	14	F	1 systolic	3rd & 4th lis	—	—	50	4	Anemia	—
29	15	M	1 systolic	3rd lis	8.5	6.3	50	3	Anemia	Anemia
30	5	M	1 systolic	lsm	6.5	5.0	60	3	Anemia	Anemia
31	5	M	1 systolic	lsm	—	—	60	2	Anemia	—
32	6	F	1 systolic	1st & 2nd lis	—	—	60	2	Anemia	—
33	10	F	1 systolic	2nd lis	—	—	70	2	Anemia	—
34	52	M	1 systolic	4th lis	12.5	8.0	70	2	Anemia	Anemia
35	10	M	1 systolic	2nd & 3rd lis	—	—	70	1	?Anemia	—

were heard. Thirty-five individuals had systolic murmurs of some intensity. Of these, two had apical diastolic murmurs as well. The location and intensity of these murmurs is given in chart 2. In this group of 35 individuals 29 had systolic murmurs of grade 1 or 2 intensity associated with hemoglobin values of 70 per cent or less. Malaria was hyperendemic in this area as evidenced by spleen survey and blood smears, and hookworm infestation was found in 24 per cent of all individuals studied in these villages.<sup>2</sup> The operation of at least these two factors made anemia quite a common finding in this group. It is well established that anemia can produce systolic murmurs and cardiac dilatation.<sup>3, 4, 5, 6, 7, 8, 9</sup> Therefore, the murmurs found in this group of 34 individuals having only grade 1 or 2 systolic murmurs were not considered diagnostic of valvular disease but were arbitrarily ascribed to the anemia.

There were four individuals whose systolic murmurs were regarded as "unexplained." The first was a girl of 12 (Case 3) with a harsh grade 3

systolic murmur at the base of the heart maximal at the left of the sternum, a palpable thrill in the same area, and a grade 2 systolic murmur at the apex. The position of the maximum impulse (PMI) was located 3.5 centimeters to the left of the midclavicular line (MCL) in the fourth left intercostal space. The hemoglobin value was 50 per cent and the splenic index 3. Although aortic stenosis was suspected, that diagnosis was not hazarded in view of the anemia. The second was a boy of 14 (Case 4) with slight cardiac enlargement, grade 2 systolic murmur at the apex, an independent systolic murmur along the left sternal margin, a hemoglobin of 70 per cent, and a splenic index of zero. His mother said that he had been incapacitated because of pains and swellings in his joints for several months when he was seven years old. This patient is regarded as one who, on being followed for a number of years, might well eventually develop unequivocal evidence of organic valvular disease. The third was a girl of 16 (Case 5) with grade 2 systolic murmurs at apex and base, a booming first heart sound at the apex, a third heart sound at the apex, no cardiac enlargement, hemoglobin 70 per cent, and splenic index zero. She is the sort of patient who would probably be listed as "possible heart disease" in a Cardiac Clinic. The fourth was a boy of 13 (Case 6) with a grade 1 musical systolic murmur at the apex, no cardiac enlargement, hemoglobin 80 per cent, and splenic index 1.

Two patients in the group had definite evidence of organic rheumatic valvular heart disease. The first, a girl of 10 (Case 1), had a grade 1 systolic murmur and a definite long mid-diastolic rumble at the apex. The apex impulse was in the midclavicular line, the hemoglobin 50 per cent and the splenic index 3. The second was a boy of nine (Case 2) with a grade 2 soft systolic murmur at the apex, another grade 2 systolic murmur in the second and third intercostal spaces just to the left of the sternum and a definite long low-pitched mid-diastolic rumble at the apex culminating in a sharp presystolic crescendo whip and a booming first heart sound. The apex impulse in this case was 2 centimeters to the left of the midclavicular line in the fourth interspace, the hemoglobin 70 per cent, and the splenic index 3. In the absence of evidence that anemia can produce the diastolic rumble characteristic of mitral stenosis, each of these individuals was regarded as having organic mitral stenosis, and, surely the second, mitral insufficiency as well.

At this point it may be interpolated that following the studies at Uritai and Seapiapi a visit was made to Kerema, further along the Papuan Gulf. At the Angau Native Hospital there the writer was shown a case diagnosed as endocarditis by Sgt. James M. McKerrell, E. M. A. (European Medical Assistant). The patient, a man of about 35, had mitral stenosis and insufficiency and aortic insufficiency with auricular fibrillation, apparently of recent origin and the cause of his admission. Including the patient seen at Lae and the two children at Uritai and Seapiapi, this brings to four the number of natives of New Guinea in whom the diagnosis of rheumatic heart disease was made.

*Cardiac Enlargement without Heart Murmurs.* In nine individuals without heart murmurs the apex impulse was felt to the left of the mid-clavicular line (chart 3). In six the enlargement was attributed to anemia. In three the enlargement was unexplained. Two individuals in the latter group had peripheral arteriosclerosis.

*Blood Pressure Determinations.* The systolic blood pressure determined in 137 individuals 11 years of age or older varied from 106 to 162 with a mean of 106 millimeters. The individual with a systolic pressure of 162,

CHART III  
Cardiac Enlargement in Nine Individuals without Heart Murmurs

No.	Age	Sex	PMI	MCL	HB %	Splenic Index	Interpretation of Enlargement
36	40	F	9.0	6.5	50	2	Anemia
37	12	M	8.5	6.5	60	3	Anemia
38	5	F	6.5	5.5	60	1	Anemia
39	13	M	8.5	6.0	60	2	Anemia
40*	18	M	11.5	7.5	70	0	?Anemia
41	14	M	8.5	7.0	70	2	?Anemia
42	37	M	9.0	7.5	80	0	Unexplained. Peripheral arteriosclerosis. BP 114/78
43	47	M	8.5	7.5	80	0	Unexplained. Peripheral arteriosclerosis. BP 106/62
44	24	M	11.0	6.8	80	0	Unexplained

PMI = Position of maximal cardiac impulse to the left of the midsternal line.

MCL = Distance from midsternal line to midclavicular line.

\* Numbers 9, 11, 16 and 40 were siblings. A third sister had a normal heart without murmurs.

a man of 62, was the only one in the entire group whose systolic pressure exceeded the "normal range." His diastolic pressure was 78 millimeters. In the entire group the diastolic pressure varied from 40 to 90 millimeters with a mean of 65 millimeters. Two individuals had "borderline" diastolic pressures. One was a girl with a blood pressure of 120 mm. Hg systolic and 90 mm. diastolic. The other was a 40 year old man with slightly thickened brachial and radial arteries and a blood pressure of 120 mm. Hg systolic and 90 mm. diastolic. As shown in chart 4 the range of blood pressures and the

CHART IV  
The Blood Pressure of 137 Papuan Natives

Age Group	11-25 Years	26 Years and Older	Total
Number of Individuals Examined	81	56	137
Systolic Blood Pressure			
Maximum	132 mm.	162 mm.	162
Minimum	82	85	82
Mean	105	106	106
Diastolic Blood Pressure			
Maximum	85	90	90
Minimum	40	50	40
Mean	65	62	65

mean blood pressures were essentially the same when the group was "broken down" into two age groups: 11 to 25 years of age, and 26 years of age or older. The figures were also practically identical when considered by sex.

There were 38 individuals in the entire group with a systolic pressure of 100 millimeters Hg or less. In this group the systolic pressure ranged from 82 to 100 with a mean of 95 millimeters, and the diastolic between 50 and 76 with a mean of 60 millimeters. In the group of 137 individuals in whom the blood pressure was taken then, 27.7 per cent had hypotension. These figures were closely approximated in both age and sex groups.

*Vascular Disease.* Some degree of thickening and tortuosity of the brachial, radial, temporal or dorsalis pedis arteries was noted in 29 individuals. In 16 it was slight and in 13 moderate in severity. All but two of these were males. The exceptions were a woman of 39 with moderate and one of 46 with slight peripheral sclerosis. The age distribution of individuals with sclerosis of the peripheral arteries is shown in chart 1.

In contrast to the frequency of peripheral arteriosclerosis were the ophthalmoscopic findings. None of the 56 individuals 26 years of age or older showed retinal vascular changes. Ophthalmoscopic examination was not carried out in the younger age groups.

*The Meteorological Background.* In view of the alleged relationship between climate and rheumatic fever it was considered of interest to review the meteorological features of this part of the Papuan coast. The writer is indebted to the 15th Weather Squadron, 42nd Weather Station, AAF, for supplying the data given below.

1. Rainfall. There is considerable variation in the amount of rainfall along the Papuan coast. The vicinity of Port Moresby is the driest with an annual average of 40 inches. Proceeding along the coast there is a steady increase in the annual fall reaching a peak at Kikora, at the head of the gulf. Figures are available from the stations at Kairuku on Yule Island, approxi-

CHART V  
Monthly Averages of Rainfall (in Inches) over a 20-23 Year Period

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Year
Kairuku	9.99	10.28	8.56	5.22	1.53	2.11	1.03	0.65	1.62	1.54	2.92	5.59	54.04
Kerema	9.44	8.09	10.68	11.26	16.92	16.33	13.12	13.93	12.47	12.32	9.27	7.35	141.18

mately 60 miles, and from Kerema (chart 5), approximately 130 miles northwest of Port Moresby. The villages studied, Uritai, and Seapiapi, lie about halfway between these two stations.

Moving Northwest along the coast to Kerema there is a sharp increase of annual rainfall due to certain topographical conditions. The dry and wet seasons are less pronounced, there being considerable rainfall even in the so-called dry season. As the isohyetal map (figure 1) shows, the annual rainfall in the Uritai-Seapiapi region is about 100 inches.

2. Temperature and Humidity. Along the coast of Papua, daytime maximum temperatures show a definite, though small, monthly variation, being highest in the months of November to March and lowest in June, July and August. The annual range of maximum temperatures averages about 8 degrees (F.) over all coastal stations.

Over the Papuan coastal regions the humidity is uniformly high, rarely falling below 70 per cent. Kerema (chart 6) is the only station in the area under discussion for which any data on temperature and humidity are available. It is obvious from these figures that we are dealing, in the region studied, with a hot humid climate with relatively little variation.

CHART VI  
Temperature and Humidity at Kerema

	Yrs. of Record	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Year
Mean of Daily Max. Temps. (deg. F.)	11	90.2	90.3	89.6	88.1	86.8	84.8	83.8	83.4	84.8	86.8	88.6	90.1	87.3
Mean of Daily Min. Temps.	11	73.8	73.7	74.2	74.4	74.3	73.7	72.5	72.6	73.3	74.2	74.1	74.1	73.7
Relative Humidity at 9 a.m. (%)	16	79	77	79	80	84	86	86	87	86	84	80	80	82

*Dietary Considerations.* Living as they do on a diet of sago, a few tropical vegetables and fruits such as cocoanut, breadfruit, pawpaw and limes, no milk, some fish, and meat only on very rare festival occasions, it seems likely that these people suffer from some degree of dietary deficiency of one type or another. Unfortunately, a careful search was not made for clinical evidence of vitamin deficiency, but chance observations were occasionally made of rachitic deformities of the chest and perlèche.

#### COMMENT

Cardiac enlargement and systolic bruits of the type described above have been observed in the anemia of hookworm disease<sup>9</sup> and chronic malaria.<sup>6, 7</sup> In view of the fact that most of the individuals in the surveyed group had malaria and many also had hookworm infestation, it seems likely that most, if not all, of the systolic murmurs detected are attributable to these causes. In one investigation<sup>10</sup> soft blowing diastolic murmurs have been ascribed to severe anemias, but there is no convincing evidence that rumbling mid-diastolic murmurs or presystolic crescendo murmurs are attributable to anemia. It seems tenable then that all four of the individuals described actually had organic mitral stenosis.

The observations presented on the blood pressure and vascular status of these individuals are obviously too limited to warrant general conclusions, but the cases of valvular heart disease, by virtue of their mere existence in any number in this limited series of cases, seem worthy of comment. It is



quite well established that the percentile incidence of rheumatic fever and rheumatic heart disease is smaller in the southerly than in the northerly regions of the United States.<sup>11, 12, 13, 14, 15, 16, 17</sup> These conditions have been regarded as diseases of cold, damp and stormy<sup>16</sup> environments and their inception in the tropics has been regarded as questionable<sup>18</sup> or extremely rare and with mild manifestations and less striking sequelae.<sup>19, 20</sup> In recent years, however, there have appeared more and more case reports of rheumatic fever and rheumatic heart disease in tropical<sup>21, 22, 23, 24, 25</sup> or semitropical<sup>26, 27, 28</sup> regions. The extreme view has even been taken<sup>23, 27</sup> that they are as frequent in the tropics as in the temperate zones. Autopsy statistics on this point are meager. Major T. C. Backhouse<sup>29</sup> in a series of about 1400 necropsies performed at Rabaul from 1925 to 1940 found two cases with fish-mouth mitral valves. Microscopic examination of one of these hearts in Australia showed typical Aschoff bodies. The available literature reveals only one previous report of rheumatic heart disease in New Guinea.<sup>30</sup> This was in a youth of 18 in cardiac failure in whom physical examination suggested mitral stenosis, the origin of which was regarded as a mystery.

Streptococci are regarded as involved in one way or another in the natural history of rheumatic fever, but data on their incidence in the pharyngeal flora of healthy residents of the tropics or those suffering from acute infections of the upper respiratory tract, are contradictory. Beta-hemolytic streptococci were cultured far less frequently in Puerto Rico than in New York City<sup>31</sup> and much less frequently from natives of Rabaul<sup>29</sup> and from white troops in Australian<sup>29</sup> and American<sup>32</sup> general hospitals in the Mandated Territory of New Guinea than in temperate regions, but Norris<sup>33</sup> found beta-hemolytic streptococcus 77 times in 272 cultures from cases of upper respiratory tract infection among the armed forces in the South Pacific. Further clinical, pathological and bacteriological studies along these lines might throw some light on the still highly controversial subject of the etiology of rheumatic fever.<sup>34</sup>

#### SUMMARY AND CONCLUSIONS

1. Four cases of mitral stenosis were observed in Papua and the Mandated Territory of New Guinea. Two of these were detected in a cardiovascular survey of 200 native Papuans living in a hot damp environment. The other two, who were patients in native hospitals, also had auricular fibrillation.

2. Rheumatic heart disease is apparently uncommon, but by no means rare, in natives of eastern New Guinea.

3. It is felt that the more carefully people in the tropics are studied, the more universal will rheumatic heart disease be found to be.

4. Systolic murmurs and palpable cardiac enlargement, explicable on the basis of anemia, were frequently detected.

5. Despite the apparent absence of retinal vascular disease and infrequency of hypertension, the population ages prematurely. This is apparently

due to the prevalence of the infectious tropical diseases of youth rather than to the degenerative changes of middle age.

Addendum: Two interesting contributions have appeared in the literature since this article was written. The writers of the first paper<sup>35</sup> in describing 20 cases of rheumatic carditis among 1307 autopsies at Curaçao, Netherlands West Indies, rightly insist that the true incidence of rheumatic carditis can be determined only by collecting reliable data, based especially on autopsies with histological examinations. The authors of the second paper<sup>36</sup> raise the question of an actual increase in the incidence of rheumatic fever in Panama since about 1927.

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# THE DOCTOR AS A WITNESS \*

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## THE DIFFERENT CAPACITIES IN WHICH THE DOCTOR MAY BE CALLED TO TESTIFY

THERE are three different sets of circumstances under which a doctor may be called as a witness and the rights, privileges and duties of the doctor will be found to vary with those circumstances. They are as follows:

1. Where the doctor is possessed of information relevant to some issue in the case, which information he acquired in other than a professional capacity. Example, the doctor, while driving to make a call, sees an automobile hit a pedestrian. The pedestrian sues the automobile owner for damages for negligence. The doctor may be called by either party to testify on the issue of negligence.

2. Where the doctor has treated a patient and he is called upon to testify as to the physical condition of the patient, the treatment administered, etc.

3. Where the doctor has never treated the person whose bodily condition is in issue but is called as an expert to assist the court in arriving at the determination of a scientific fact as to the bodily condition of such person, the expectation as to his recovery, etc.

Of course, the doctor may often be called as a witness in more than one of the above capacities. In the example mentioned as capacity No. 1, the doctor who sees the pedestrian hit may stop and treat the injured man. In capacity No. 2, the doctor, in addition to testifying as to his treatment of the patient, may be called upon to advise the court as to his opinion of the present condition of the patient and the expectation of his recovery.

Nevertheless, the above distinctions as to the capacity in which the doctor is to be called upon to testify must be borne in mind in determining certain questions as to his duties, responsibilities and privileges as a witness.

## THE DUTY OF THE DOCTOR TO TESTIFY

It is the duty of every citizen to testify when called upon by a court of law, regardless of any personal inconvenience to the witness, and this duty may be enforced by a court writ known as a "subpoena," a writing served upon the prospective witness commanding him to appear and testify in a certain court in a certain cause and on a certain named day. Although there is some question whether a doctor may be compelled to testify in capacity No. 3 without extra compensation (this question will be discussed later), as to capacities 1 and 2 the doctor is no different from any other man

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and *must* respond when summoned regardless of other professional engagements.

The manner of service of the subpoena varies in different jurisdictions. It is usually served by a court officer but may be served by any person, including the litigant himself or his attorney. The service must be accompanied by the tender to the witness of the statutory fees, so much for each day's attendance (a small amount, usually \$1.50 or so), plus mileage from the place of residence of the witness to the courthouse. The failure of the witness to respond to the summons contained in this writ is punishable as contempt of court, the punishment being either a fine or imprisonment.

Attorneys generally realize that the doctor is a very busy man, who should not be compelled to sit around a court-room, day after day, waiting to be called to the stand, and they will usually be considerate in informing the doctor that he need not appear at the exact time named in the subpoena but that if he will promise not to go out of town without letting the attorney know in advance that he is to be away and will arrange that no matter where he is he can be reached by telephone on short notice, the attorney will arrange to telephone him when he is actually needed. If the subpoena is served by someone other than the attorney, the doctor should telephone the attorney and endeavor to make the arrangement above suggested. If, however, the attorney is unwilling to so arrange, the doctor must be there at the court-room at the time named, regardless of the other calls upon his time.

When the doctor reaches the courtroom and is not called to the stand right away he should get in touch with the attorney at the first recess (there is usually a short recess in a trial in the middle of the morning and in the middle of the afternoon, as well as the recess at noon and that at the end of the day) and ask the attorney to call him to the stand as soon as possible so that he can get back to his patients. Often under such circumstances the attorney will obtain leave from the judge to call the doctor out of turn, sometimes, for such purpose, temporarily withdrawing from the stand another witness whose examination has not yet been concluded.

To reassure the doctor who has never been a witness and who may find himself dreading what he considers as an ordeal, it should be explained that very rarely is a doctor ever called to the stand "cold," without ever having gone over with the attorney the matter of what his testimony is to be. Usually there will have been at least one conference between the two, often more than one, in which conference the doctor will have been advised as to the questions that will be asked him and will have told the attorney what his answers to such questions will be. If the issue is an important one, where the reputation of the doctor may be in any way at stake, the doctor should insist on having such a preliminary conference.

#### PRIVILEGE NOT TO TESTIFY

As stated above, the doctor has a duty to testify when called upon. Has he a *privilege* not to testify?

The answer to the above question is that the one certain privilege of the doctor is the privilege of any witness not to be compelled to answer a question put to him when the effect of that answer may be to incriminate the witness. This, it will be noted, is not a privilege to refuse to take the stand, but a privilege to refuse to answer a certain question. As to whether an answer to a question might incriminate him is for the witness himself to decide. The method of claiming such privilege is very simple. The witness says to the judge, "I decline to answer such question on the ground that the answer might tend to incriminate me."

There is also, in certain jurisdictions, a privilege of the witness not to answer the question if the effect of the answer will be to disgrace the witness, although not actually to incriminate him. The ruling on such claim of privilege will depend upon whether the judge considers the question relevant to some issue in the case. If it is relevant, the answer can be compelled. If it is not relevant, the claim of privilege will be sustained.

As has been stated, the above are the only privileges of the doctor. What about what is popularly known as the doctor-patient privilege? That is the privilege of the patient only and it in no way belongs to the doctor.

In discussing the doctor-patient privilege it should first be pointed out that such privilege is not a so-called "natural" privilege recognized by the courts from ancient times but is a privilege that exists only because so ordered by a particular legislature. It exists, if at all, only by statute, and its extent is exactly measured by the language of the particular statute. A statute on this subject will be found to have been enacted in something over one-half of the states of the Union and, as these statutes will be found to differ somewhat in their terms, an explanation of the rule on this subject in a given jurisdiction will have to depend upon a study of whether there is a statute on such subject in that jurisdiction and what its language is.

Many of the statutes are, however, fairly similar in their wording and a general idea of such legislation can be gained by examining the statute of New York, which was the first state to legislate on this subject. It reads as follows:

"A person duly authorized to practice physic or surgery, or a professional or registered nurse, shall not be allowed to disclose any information which he acquired in attending a patient in a professional capacity, and which was necessary to enable him to act in that capacity; unless, where the patient is a child under the age of sixteen, the information so acquired indicates that the patient has been the victim or subject of a crime, in which case the physician or nurses may be required to testify fully in relation thereto upon any examination, trial or other proceeding in which the commission of such crime is a subject on inquiry."<sup>1</sup>

Analyzing such statute it will be noted

(1) The statute applies only to persons duly authorized to practice medicine or surgery, or a professional or a registered nurse.<sup>2</sup> The person consulted must be a professional physician in the usual sense of the word.

It does not include a veterinary surgeon or a pharmacist. In view of the modern recognition of dental science as a branch of medical science it should include a dentist, although there is authority to the contrary.<sup>3</sup> It includes a practitioner of any branch or school of medical science recognized as such by the law or the reputable medical profession. Whether it applies to a licensed osteopath or chiropractor is a matter of dispute.<sup>4</sup>

(2) The consultation with such a person must be had in his professional character at the time. A consultation for some purpose other than that of ultimate curative or alleviative treatment is not privileged; nor is a communication made at some time when the professional relation is not pending. A communication made to a medical practitioner invited to an inspection or consultation at the opponent's instance is not privileged, because it is not usually made for the purpose of curative treatment,<sup>5</sup> although if such practitioner does undertake to administer treatment the privilege does attach.<sup>6</sup>

(3) The information acquired must have been necessary to enable the doctor to treat the patient. The word "information" has been broadly construed so as to include data furnished through submission to inspection as well as oral communications.<sup>7</sup> But it is the tenor or substance of the communication only that is privileged. The mere fact of making a communication as well as the date of a consultation and the number of consultations are therefore not privileged from disclosure so long as the subject communicated is not stated.<sup>8</sup>

Statements made to the doctor which were not necessary as the basis for any treatment to be administered are not privileged. For example, a person injured in a street accident who is picked up by an ambulance tells the ambulance surgeon en route to the hospital the story of how the accident occurred. The disclosure is not privileged.<sup>9</sup> A doctor called to give first aid to a person injured in an automobile collision was allowed to testify that he noticed the odor of liquor on the man's breath.<sup>10</sup>

The privilege exists regardless of whether the doctor received any compensation for his services or rendered them with any expectation of receiving compensation.

As previously stated, the privilege is that of the patient, not of the physician. The latter cannot claim the privilege if the patient is willing to waive it. The waiver may be made in a number of ways. It may be expressed or implied. The patient may waive it on the trial. He may waive it in advance of the trial and in advance of any litigation by consenting in an application for a life or accident insurance policy that any conversation had with the physician regarding the physical condition shall not be privileged.<sup>11</sup>

The patient may waive the privilege by his conduct, this involving what the law calls an "implied waiver." As the whole theory of the privilege is based upon the patient's supposed unwillingness that his ailment should be exposed to the world at large, where the patient himself discloses to the world his physical condition the privilege should no longer be recognized. For example, the patient himself calls the doctor to the stand and examines

him regarding his physical condition; or the patient requests the doctor to act as a witness to his will, knowing that the doctor will be called upon to testify as to the patient's physical condition when the will is offered for probate; or the patient calls another doctor to the stand to testify as to the patient's physical condition; or a patient sends in a doctor's certificate as part of his proof of claim for benefits under an accident insurance policy; or his beneficiary sends in such a certificate with his proof of claim on a life insurance policy; or a patient sues a physician for malpractice. In all these cases it can be logically contended that the privilege has been waived, although the courts have not been consistent in so holding.<sup>12</sup>

The privilege between doctor and patient survives death, but it can be waived by the executor, administrator, or an heir of the decedent. It may also be waived by the guardian of a minor or of an insane person.<sup>13</sup>

As heretofore stated, the existence of the privilege and its extent will depend in every case upon the decision of the legislature as to whether it wishes to pass such a statute and how far that statute should go. It will be found, also, that even in a state which has established the privilege, the legislature has almost invariably made it inapplicable to workmen's compensation cases, and modern sanitary legislation has also abolished the privilege, in part, for venereal diseases and for narcotic drugs.<sup>14</sup>

The above explanation as to the law of privilege has been given for the benefit of a doctor reader, but it is not at all necessary that he should attempt to make himself familiar with the rules on this subject or their distinctions. Usually the patient will be a party to the law-suit. If he himself calls the doctor as a witness there is no difficulty, as he declares himself thereby as being willing to have the doctor testify. If the opponent calls the doctor as a witness, the counsel for the patient will himself make the objection unless he is willing that the privilege be waived. The only situation for which the doctor must be on the look out is the one where the patient is not a party to the cause and there is no other party to look after his interests. In that case the doctor will listen to the question addressed to him and if, in his opinion, it calls for a conversation with the patient that might be privileged, he will simply turn to the judge and say, "Your honor, I doubt if I ought to answer that question in view of the fact that it calls for a statement that I consider privileged." The judge will either say, "You need not answer," or he will explain that the testimony called for is, for some reason, not within the privilege rule and he will instruct the witness to answer. If so instructed by the judge, it will be the duty of the witness to answer the question and he can do so without any disturbance of conscience. Whether there is a privilege against disclosure under those particular circumstances is purely a question of law and on that question the person to decide is the judge.

#### HOW A WITNESS IS EXAMINED IN A LEGAL PROCEEDING

The term "legal proceeding" is used in the above heading advisedly instead of "court," for a doctor will be called as a witness not only before courts



but before coroners in their inquests, before administrative tribunals, such as industrial accident boards, and in statutory proceedings for the commitment or release of the insane. In general, the method of examination of the doctor as a witness will be the same in all proceedings, the only difference being that before administrative tribunals the proceedings are likely to be less formal and the rules of evidence are much less strictly applied than in a court. Also there is often less technicality applied when the hearing is before the judge sitting as the sole trier of fact than when the case is tried before a judge and jury. In the last named case the jury decides all questions of fact. The judge decides all questions of law.

In any form of legal proceeding, the witness is first sworn to tell the truth and is then examined by the party calling him. The examination is by question and answer. The questions are usually short, if calling for some specific fact, but sometimes a question will be put in a broad form, such as, "When you went to the patient's house on the day you mentioned please tell us what happened?" To this question the witness will give what is called a "narrative" form of answer, going ahead with a story of what did happen until he finishes or is interrupted by the judge or by counsel. A familiar form of question put to a doctor which calls for a narrative reply would be, "When you first saw the patient on the day you have stated what did you find his condition to be?"

### OPINION EVIDENCE

Facts are called for and not the opinions or conclusions of the witness. The reasons for this rule are obvious. The function of the trier of fact, whether the judge sitting alone or the jury, is to reach the proper conclusion from the facts of the case. Therefore, as a basis for his conclusions what this trier of facts wishes are facts, not opinions. For example, in a suit for damages for negligence arising out of an automobile collision, a witness can never be asked, "Was the defendant negligent?" Negligence is a conclusion, often reachable only on the basis of many facts. The information that the court does wish from the witness is, "What did the defendant do?" "How fast was he driving?" "What was the condition of the traffic light?" "Where was the plaintiff?" "What was he doing?"

There are certain matters, however, on which the trier of facts is not able to reach a conclusion without help from someone, for no matter how many facts may be brought to his attention he will not know how to apply such facts so as to reach a correct conclusion. These are mainly cases where scientific principles are involved and the law not only permits but welcomes help from men versed in that particular science to aid the trier of facts in arriving at a proper conclusion. This help can be given not only in instructing the court as to the principles of the particular science but in giving the court the opinion of the witness as to the proper conclusion from the fact under the rules of that science. If the witness knows more than does

the court about a science whose principles are involved in the issue on trial, he is an "expert witness." An expert need not be filled with book learning. He may have acquired his special knowledge by long experience. Also there are, of course, borderline cases where it is difficult to determine whether the question is one for expert opinion or not, whether by general experience the jury do not know a simple scientific fact anyway without asking for aid. For example, a man loses a finger on a circular saw and the issue is his own carelessness. Is it a scientific fact on which a court will receive opinion testimony that when a saw is whirling the outer edge is invisible to the eye, or is that something which every jurymen knows and on which expert testimony is not needed?

#### OPINIONS BY MEDICAL EXPERTS

On medical questions, however, there is never any doubt as to the necessity of receiving opinion testimony. Any doctor, by reason of his training, is competent to advise the trier of fact as to the intricacies of the medical art and is therefore an expert witness. The doctor need not have had any experience of his own on the particular medical question involved in the case. His education and training alone fit him to act as an expert. Nor does he need to be a specialist in any particular branch of his profession. He does not have to be an orthopedic surgeon to testify as to the proper way to set a broken limb, nor a psychiatrist to testify as to the sanity of a patient. The more experience a doctor witness may have had and the more learned he is in the particular field the better, but this goes only to the weight of his testimony, not to the admissibility of it.

#### HEARSAY EVIDENCE

Another rule of the law of evidence is that what the court wishes to hear is what the witness himself knows, not what he may have heard from others. This is what is called the rule against hearsay. Ordinarily a witness cannot testify, "I know it is true because John Smith told me." The court will say, "We do not want to get this second-hand from you. Produce John Smith and let him tell his story here so that he may be cross-examined upon it."

The hearsay rule is not an absolute one, however, for there are certain matters that may not be susceptible of proof in any other manner than by hearsay. For example, a man cannot ordinarily tell how old he is or who his parents are except by hearsay. Therefore the law has had to create an exception to the hearsay rule, which exception is known as the "pedigree" rule. Statements of deceased members of the family as to family relationships are admissible even though hearsay. There are various other established exceptions to the hearsay rule but there are only four of these exceptions in which the doctor will ordinarily be interested.

One of these is this same rule as to pedigree. If a patient who later died told the doctor that X is her illegitimate son the statement will be admitted.

Another exception is the fact that on scientific matters on which the witness is called to testify he need not have acquired his knowledge through experience. He may have acquired it from books.<sup>15</sup>

The third exception is that where the doctor has obtained from others the information on which he based, in part at least, the treatment administered, he is generally permitted to testify as to such statements made to him. These statements may consist of three classes:

(1) Statements made by a patient to a doctor as to his present symptoms or exclamations of the patient showing present pain. There is no question about the admissibility of these statements.

(2) Statements by a patient to a doctor as to past symptoms. On this the courts are not in agreement, although the modern tendency is to favor admissibility.

(3) Statements made to a doctor by third persons. Here, again, the courts are not in agreement, but where the information comes from an attending nurse or another physician or from the wife or some other member of the family having personal observation and an interest in learning and describing accurately, there seems every reason for admitting testimony based in part on these statements.<sup>16</sup>

#### DYING DECLARATIONS

The fourth exception to the hearsay rule that the doctor will encounter is the dying declaration. Early in the history of the law of evidence it was decided by the courts that a statement made by a man about to face his Maker had such a ring of truthfulness about it as to warrant the court's receiving it even though a second hand report of the statement by one who heard it made is hearsay in nature.<sup>17</sup> The courts have seen fit to limit the application of the rule to but one class of cases, i.e., criminal prosecutions for homicide where the death of the declarant is the subject of the charge, but in those cases the rule is generally applied. Before the dying declaration can be admitted, it must be proved that the declarant, at the time that he made the statement, believed that he was going to die and the statement made must be one of fact and not of opinion. Therefore a doctor who is to listen to a dying declaration by a person suspected to have been injured by violent means so that he is in danger of death should take pains, by questions addressed to the patient, to ascertain, before the dying declaration is made, that the patient really believes that he is going to die. And, when the dying declaration is made in the form of an opinion or conclusion, questions should be asked by the doctor to bring out the facts that are the basis for the conclusion.

For example, as a dying declaration may be used to absolve a defendant from the charge of crime as well as to convict him, assume the following conversation between doctor and patient:

Patient, "I want to tell what happened."

Doctor, "Why, do you believe that you are going to die?"

Patient, "Yes, Bill shot me but it wasn't his fault." ("Not his fault" is a conclusion.)

Doctor, "Why wasn't it his fault?"

Patient, "He was shooting at a rabbit and didn't see me so near."

Going back to the description of the trial, when the party calling the witness concludes his examination he turns the witness over to the opponent for cross-examination. When the cross-examination is concluded the party who called the witness may again interrogate him to clear up matters brought out in the cross-examination. This is called "redirect" examination. When the redirect examination is concluded, the witness is through and may leave the stand. Some attorneys, however, are very cautious and selfish in insisting that the witness stay around as they may wish later on to ask him some more questions. If such a request is made and the doctor is a busy man who wishes to get back to his patients, he should not hesitate to tell the judge how busy he is and ascertain if the judge will not see to it that the witness is reexamined right then and there or else released from attendance.

#### QUALIFICATION OF DOCTOR AS EXPERT WITNESS

As pointed out in the opening of this paper, there are three capacities in which the doctor may be called to testify: (1) as an ordinary witness who saw something happen, (2) as the doctor who treated the patient, (3) as an outsider called in to give his opinion on a problem of science. Capacity No. 1 presents no problem other than those that confront any witness. In Capacity No. 2 there is every expectation that the doctor will also be called upon to testify in Capacity No. 3. Therefore the attorney who calls the doctor will, right at the beginning, plan to qualify him as an expert. This will be by a series of questions planned to draw out the intellectual and scientific training of the doctor and his experience, if any, in the particular field under inquiry. These questions will be somewhat as follows: Please state your name? Where do you reside? What is your profession? What has been your general education? What medical school or schools have you attended? In what hospital did you interne? How long have you practiced medicine? Where? What has been the nature of your practice? Are you now connected with any hospital? Have you ever had any experience in treating fractured bones? What has that experience been? Do you belong to any medical or scientific societies? What are they?

Sometimes the attorney will simply ask the doctor a few preliminary questions and then ask him to state his qualifications as a medical man. The writer considers this practice unwise. A glib answer, reciting a long list of schools attended, membership in learned societies, breadth of practice, etc., will practically always place the witness on the defensive with the jury, as

being patently a man who makes his living by giving expert testimony, "an old hand at the game," to be carefully watched. It is much better for the attorney's case and for the appearance of the witness in the eyes of the jury to have these facts drawn out of the witness by a series of questions.

In this examination (which is called an examination on *voir dire*, being an examination to determine the qualifications of the witness as an expert) the witness should take pains not unduly to stretch his qualifications as an expert, for he may be cross-examined on that point. If he is a young practitioner who never set a leg in his life until he was called to this particular patient, let him not claim to be an experienced orthopedist. If asked as to whether he has treated similar cases, let him not answer, "Yes, dozens of them" for 24 is quite a large number and when the cross-examiner begins to ask him to state just what particular cases of this kind he did treat, when he gets through he may be able to recall only 5 such cases and that is embarrassingly less than 24.

On the other hand, of course, the doctor must not be too timid and modest about his qualifications. He should give the impression of a man who knows his profession but has no desire to brag about his qualifications or unduly exaggerate them.

#### METHOD BY WHICH EXPERT WITNESSES ARE EXAMINED

Let us first discuss the testimony of the doctor in Capacity No. 2, the man who treated the patient. After describing his diagnosis and the treatment which he administered, he may be asked the question, "From your knowledge of medicine and your experience in this case, what is your opinion as to the present condition of the plaintiff being permanent?" Doctor: "I believe that the condition will be permanent." Question: "What reasons do you have for such opinion?" The witness will then state the reasons which led him to the conclusion reached.

When, however, the witness testifies in Capacity No. 3 as an outsider who never treated the patient but who has been called as an aid to the court in determining scientific principles, or scientific conclusions from facts, he must be examined in a rather unusual manner, by being asked to answer one or more hypothetical questions based on some evidence already offered in the case. The following is an example of such a question:

"Let us assume, Doctor, a man of thirty years of age, who had prior to June 8, 1932, enjoyed good health and was physically strong, and that on the morning of June 8, 1932, he was seated in the back seat of an automobile traveling along a public highway at about twenty to twenty-five miles an hour, and that an automobile turns into the road upon which this car is traveling, and collides with the rear of the car in which the plaintiff is riding, and that he is thrown from his seat in the rear of the car up against and through the glass windshield, and receives a V-shaped cut on the left side of the face running in a position from the nose downward and then upward toward the ear, and that a splinter of steel pierces the spine at or near the base; that severe cuts and wounds are received on the chest and legs; that the plaintiff, bleeding

profusely from the head and legs, is taken to a hospital; that he was unconscious for six hours, that upon examination the next morning by a doctor he is discovered paralyzed in both legs, that there is no sensation whatever in his left leg; that there was a total lack of lines of expression upon the left side of the face and very slight mobility upon the right side of the face; and that he had exaggerated reflexes.

"Now assuming those facts, can you state with reasonable certainty what in your opinion was the cause of the plaintiff's paralyzed condition?"<sup>18</sup>

The reason for the use of the hypothetical question is apparent. The witness, knowing nothing about the facts of the case except by hearsay, can testify only as to the scientific conclusion which he is able to reach from the facts submitted to him. In giving his answer the witness must confine himself to the facts stated in the question. He cannot base his conclusion on those facts plus something else which he heard some witness say. Very often the facts on which the hypothetical question is based will be in dispute. In that case the opposing attorney, on his cross examination of the witness, may state the facts as narrated by his own witnesses and ask what, assuming such facts to be true, would be the opinion of the witness. To that question the witness may give as an answer an opinion exactly the opposite of his opinion given on the direct examination.

There is only one short cut to avoid the method of examination of an expert by hypothetical question. That is to have the witness on hand when another witness or other witnesses are telling their story and then ask the expert:

Question: "Did you hear the testimony given by Doctor X (or by Doctors X, Y and Z)?"

Witness: "Yes."

Question: "Assuming everything to which he (or they) testified to be true, what would be your opinion, etc.?"

Occasionally an inexperienced attorney will try this kind of a short cut:

Question: "Have you listened to all the testimony in this case?"

Answer: "Yes."

Question: "Based on such testimony, what is your opinion, etc.?"

Such a question is clearly objectionable as the testimony is probably in conflict and an answer to the question would compel the witness to decide which story to believe, which is not the function of the witness. Nor when his answer comes in will the jury know on just which of the disputed facts the opinion expressed by him was based.

#### USE OF MEMORANDA WHILE TESTIFYING

The law expects the witness to tell the court what he now remembers, not what he has written down in advance as his testimony and which he may undertake to read to the court. The law realizes, however, that there may be lapses in memory and concedes that a witness may be allowed to have his memory refreshed. This can be done in two ways. One is called "present recollection," the other "past recollection recorded."

In what is called present recollection the witness cannot remember something that has occurred. He knows it but it is dormant in his memory. Something which he sees, usually something handed to him for the purpose, it may be a hospital record, it may be an office diary, it may be a prescription written at the time, it may be a report written to an insurance company, something pulls a switch in his brain and the memory of the whole thing comes back to him so that he can lay down the paper and tell the whole story out of his own memory. This "pulling the switch" is what is called "refreshing the memory" or "present recollection."

On the other hand, at the time of the occurrence the witness may have made a written memorandum or he may have at the time read a memorandum made by someone else. He does not remember at all what the contents of the memorandum were. An examination of it fails to pull any memory switch. He does know, however, and is willing to so swear that he remembers making the memorandum or reading the same and knows that the facts stated therein were at the time true. In such cases the law permits the memorandum to be introduced into evidence based on the above evidence of the witness. This is what is called "past recollection recorded."

There are some situations, however, where the witness may wish to refer to a document and it does not refresh his recollection nor can it be established as past recollection recorded. Can he use the document for any purpose? Yes, if it has already been introduced as evidence in the case.

For example, take a hospital record. There has been a great deal of discussion by judges and law writers as to whether these records are admissible in evidence. The courts are now pretty generally agreed that they are admissible when properly authenticated as business records. (That the hospital record shall be properly authenticated is a problem for the lawyer, not the doctor. The doctor, if he wishes to use the record in giving his own testimony, need only notify the attorney of his desire to have the hospital record for use in connection with his testimony to be given. It will be up to the attorney to obtain the record and to have it properly authenticated and admitted in evidence.) Once the hospital record is in evidence the doctor witness may refer to it in his testimony with perfect freedom, for he is only discussing a document that is already before the court as evidence in the case. *But the hospital record must have been admitted in evidence before the doctor undertakes to use it in his testimony.* If the attorney has not yet introduced it in evidence he should do so before the witness undertakes to testify about it. The same rule will apply as to the use of books of account and other records, including public records, death certificates, birth certificates, etc.

#### USE OF GRAPHS, CHARTS, DIAGRAMS AND PHOTOGRAPHS

To illustrate or confirm his testimony the doctor witness may use graphs, charts, diagrams and photographs. But these documents derive their competence as evidence altogether from the fact that they are given in connection

with the testimony of a witness. Such a document, offered without an identifying witness, would not be admissible.

The following are examples of the methods by which such documents are introduced in evidence.

Question: You have described to us the relative positions in which the bones appear in a normal body and the position in which you found them to appear on your first examination of the plaintiff. To illustrate your statements in those respects have you prepared any diagrams?

Answer: I have.

Question: Will you produce them? (The diagrams are produced and marked by number as exhibits for identification, viz., so that the record will show by exhibit number what is being discussed on the examination of the witness.)

Question: I hand you plaintiff's Exhibit No. 7 for identification and ask you what it is.

Answer: It is a diagram prepared by me showing the position in which the \_\_\_\_\_ and \_\_\_\_\_ bones appear in a normal body.

Question: I hand you plaintiff's Exhibit No. 8 for identification and ask you what it is.

Answer: It is a diagram prepared by me showing the position in which I found the \_\_\_\_\_ and \_\_\_\_\_ bones of the plaintiff to be when I examined him on July 1, 1943.

Question: Are these diagrams correctly drawn?

Answer: They are.

Question: Do they properly show what they purport to show?

Answer: They do.

Attorney: I offer in evidence plaintiff's Exhibits 7 and 8 for identification.

For the introduction of a photograph the procedure might be as follows:

Question: You have testified as to the location of the railroad crossing and the location of the building which you have stated would obstruct the view to the north of one approaching the crossing from the west. I hand you plaintiff's Exhibit No. 11 for identification and ask you what it is.

Answer: It is a photograph of the railroad crossing about which I have testified taken from a point directly west of the crossing and showing the road, the railroad track, and the building on the north side of the road about which I have testified.

Question: Is this photograph a correct representation of the scene which it undertakes to describe as you remember that scene?

Answer: Yes.

It is apparent, from the theory that the chart, diagram or photograph is based on the testimony of the witness, rather than the contrary, that it is altogether immaterial by whom the chart or diagram was made or the photograph taken. The chart or diagram may be taken from a medical book, or it may be one prepared for instructing in a physiology or anatomy lecture.



The photograph may have been taken by any professional or amateur photographer. They all depend upon the credibility of the witness whose testimony they illustrate.

Although it is not necessary that the person who took a photograph be produced if the witness can sufficiently establish its correctness, it is, of course, well to have the photographer present to testify himself as to the manner in which the photograph was taken. That is particularly true where the photograph is of any part of the human body for the angle at which the photograph is taken may make a considerable difference in the effect to be given to the photographic representation.

### ROENTGEN-RAY PHOTOGRAPHS

Here are encountered problems much different from those that exist in the case of an ordinary photograph. For the proper reading of the roentgen-ray photograph depends so much upon angle and focus that the doctor witness cannot reasonably testify thereto until he has learned the conditions under which the roentgen-ray photograph was taken. Therefore the courts have had to lay down the following rules with regard to such photographs:

1. The person who took the roentgen-ray photograph must testify as a witness, (a) as to his qualifications, by training and experience, to take such photographs; (b) as to the trustworthiness and dependability of the instrument that was used; (c) as to the manner in which the photograph was taken, the position of the patient, etc.; (d) as to the identity of the photograph with the person to illustrate whose physical condition the photograph is offered.

When the doctor witness has taken the roentgen-ray photograph himself, he is the only witness needed. Where, however, the photograph is taken by another physician or by a dentist or by a technician, the person taking the photograph must appear and testify as to the above matters.

2. After the taking of the photograph has been thus established and the identity of the patient determined, it becomes the subject of the testimony of the doctor witness as to the proper interpretation to be placed upon it. For the law is well established that a roentgen-ray photograph cannot speak for itself. It must be interpreted by some person qualified by training and experience to make such an interpretation. Therefore the doctor who is to testify as to the findings established by the roentgen-ray photograph must not only qualify himself as a physician but as an interpreter of roentgen-ray photographs. He can have acquired such expert knowledge either by education or experience. The ordinary course in roentgenology given in medical schools will be sufficient to qualify the doctor although the more experience he has had in reading roentgen-ray photographs the more effective will his testimony be.

Suppose that the roentgen-ray photograph, after having been originally studied by the doctor, becomes lost? Can the doctor witness testify as to what the photograph showed? Although the courts are not altogether

agreed on that point, in most jurisdictions the doctor will be permitted to testify on such subjects after it has been proved (1) that the absent photograph is or was accurate, and (2) that it cannot be produced in court either because it is lost or is otherwise unobtainable.<sup>19</sup>

### MOTION PICTURES

Motion pictures may be offered in evidence under either of two sets of circumstances, namely: (1) To show something that actually occurred. For example, when a motion picture is taken, without the principal actor's knowledge, to expose an alleged malingerer by showing him walking in an ordinary manner. (2) To show an attempt to reproduce a past scene by having the original characters therein, or persons representing such characters, go through the motions claimed to have taken place at the time of the original scene.

It may be pointed out in the first place that judges are generally opposed to the use of motion pictures in a court trial, for several reasons: (1) They take up considerable time in the making of arrangements for the showing. (2) They divert the attention of the jury from matters which are really of more importance in the case. (3) They tend to exaggerate in the minds of the jury the facts which they are offered to prove. Also, under the circumstances involved in No. 2, where persons act out a scene that has occurred in the past, the uncertainty of the accuracy of such acting, particularly where there is a sharp conflict in the testimony as to just what did occur at that time, makes the reception of such evidence very dangerous.

It may therefore be said that rarely, if ever, will the courts permit the use of such evidence for the purpose described in use No. 2.

In the first set of circumstances, however, where the camera records what actually did happen, the judge is likely to admit the evidence, particularly if he is convinced that otherwise a fraud might be perpetrated on the court by a malingerer. Often, before the judge will make his ruling on admissibility, he will have a private showing of the film in his chambers, by which view the judge can see the importance of the evidence offered, its application to the issues in the case on trial and its apparent reliability.

Going back to the original proposition that a photograph is admissible only in connection with the testimony of a witness, either to aid in understanding the testimony of such witness or as confirmation of the testimony given, it is apparent that a motion picture is subject to the same rule. A witness testifies as to what he saw. He then testifies that the motion picture is a reproduction of what he saw.

Also, before the motion picture can be introduced in evidence it must be authenticated as a true reproduction of the scene that it depicts. This authentication need not be by the photographer himself, anymore than in the case of a still photograph. But it is the sounder practice in the case of a motion picture to have it authenticated by the photographer who took it,

who should testify as to the manner in which it was taken, the speed in frames per second, etc., as a motion picture will not reflect accurately the movements of the subject unless the projection machine in the courtroom is operated at the same rate of speed as was the camera,<sup>20</sup> and that the picture is a correct reproduction of what the witness actually saw.

#### PREPARATION, BY THE DOCTOR, FOR THE TRIAL

When the doctor is informed that he is to be called as a witness, it will be incumbent upon him to prepare himself for the examination.

If he is to be called as having treated the patient he should consult his notebooks and diary to see what he has written down regarding the case and should search his memory as to his first diagnosis and any later diagnoses, the treatment he administered, the progress of the patient under such treatment, etc. If the patient was taken to a hospital the doctor should ask to see and should study the hospital record of the case.

Inasmuch as he will also doubtless be asked to testify as an expert to give his prognosis as to the ailment treated, he should also make a careful and thorough study in his library of the medical literature on that particular subject, not only refreshing his memory on what he at one time learned but bringing himself up to date on all the modern developments in that field of medical knowledge. If his testimony is to be based at all on his own experience in treating such ailments, the doctor should look up his old notebooks and diaries so as to prepare himself for either direct or cross-examination on the extent of his experience in that field and the lessons he learned therefrom.

#### STUDY TO SIMPLIFY THE USE OF MEDICAL TERMS

Theoretically, and practically, the expert witness is there as an aid to the judge and jury in advising them of the scientific problems involved in the particular case and in helping them to apply the rules of science to the facts in that case. He can be of real value only if he can talk to the judge and jury in terms that they as laymen can understand. Unfortunately, in the average case, the medical testimony comes out in the form of a technical jargon that is almost completely unintelligible to the jury and can only be translated to them by the judge in his charge or by counsel in their arguments if they themselves understand the language used.

Sometimes this manner of testifying comes from the vanity of the witness in wishing to display his erudition. Generally, however, it is because the expert uses the language of the books and that used by him in discussing medical cases with his colleagues. It simply does not occur to him that these words are not perfectly intelligible to everyone.

The writer urges, therefore, that every doctor who is to be a witness go over his testimony in advance with the thought in mind as to each medical term used, "Is this term intelligible to the ordinary layman? If not, can I

express the same thought in language that the layman will understand even though I may not be able to convey the exact shade of meaning that I might try to obtain by the use of the more technical term?"

For example, the doctor will ordinarily be inclined to use the word "trauma." Cannot he convey substantially the same meaning by saying "injury?" Instead of "ecchymosis" cannot he say, "He had a black eye." Instead of using the technical terms to describe the operation cannot he say, "I turned back the scalp and exposed the skull."

So also, cannot the doctor express, in words more easily understood, such medical terms as ankylosis, axilla, ligation, osteitis, palpation, posterior, reduction, scapula, sternum, thorax, hypertension, etc.

If the doctor cannot think of the layman's term for a certain bone, organ or bodily condition, he can often obtain valuable help by looking up in his medical dictionary the term he plans to use and seeing whether, in the definition given, there is not some short term known to the layman.

If the doctor witness feels that no term intelligible to laymen will give the exact meaning of the technical term that the doctor would like to use, he can use his technical term and then attempt to translate it for the jury, "It is hard to define that condition by any less technical word than the one that I have used. It means \_\_\_\_\_. Very roughly you might use the term \_\_\_\_\_."

If the attorney has properly prepared his case he will have gone over the doctor's testimony with him before putting him on the stand. In that interview the doctor can call the attorney's attention to certain medical phrases he expects to use and see whether or not they will be intelligible to the most important laymen in the case, the judge and the jury.

#### THE DIRECT EXAMINATION OF THE DOCTOR WITNESS

If the attorney has properly gone over with the witness the testimony he is to give, the latter will know very well what questions will be asked him on direct examination and will have thought out the replies that he will make to such questions. The principal advice to be given him is to listen carefully to each question asked and not to undertake to give his answer until the attorney asking the question has finished and the witness is sure that he understands the question. If there is anything about the question that he does not understand he should not hesitate to have the question repeated. If he still does not understand it he should frankly say so and afford the attorney an opportunity to so reframe the question that it will be intelligible to the witness. If in a hypothetical question there is any fact missing that would be of value in formulating the opinion requested, the witness should say, "I could answer that question better if I knew so and so." If the missing fact can be supplied by the interrogator from the testimony in the case he will supply it. If not, and it is impossible to give a trustworthy opinion without the missing fact, the witness should not hesitate to so say.

## CROSS-EXAMINATION

This, unfortunately, is something that is looked forward to by every inexperienced witness as an ordeal. He has heard or read so many stories of witnesses being broken down on cross-examination that he fears the same thing will happen to him.

To reassure the doctor witness that most of his fears are unfounded, the writer will quote from an attorney whose function it has been to try to break such witnesses down. In writing a treatise for attorneys on the subject of "Medical Trial Technique," the author, an attorney of great experience in the trial of cases, says, in respect to cross examination of the medical witness:

"The more experience one has in the cross-examination of the medical witness and particularly the medical *expert* witness the more one must come to the conclusion that the cross-examination of a truthful, honest, efficient, and capable medical expert witness who is not given to exaggeration is not only dangerous but usually harmful to the trial lawyer. When this type of a medical witness is encountered, it is no wonder that the most experienced and most successful trial lawyers in personal injury cases frequently make the statement that the best cross-examination of such a witness is no cross-examination. It is only when the witness is neither truthful, honest, efficient, nor capable—and is given to exaggeration that one can expect to successfully destroy a witness' story by cross-examination."<sup>21</sup>

If the opposing counsel does decide to cross-examine it may be for any one of numerous reasons.

He may decide only to weaken the testimony of the witness in the eyes of the jury by showing that he has an interest in the case, e.g., that he has a large bill for attendance on an indigent patient which bill will never be paid unless the patient recovers damages in this suit; or that he is being paid a large fee for testifying; or that he is a "professional" expert spending a large amount of his time in court as an expert witness in actions for personal injuries or in will cases if the doctor is a psychiatrist or neurologist.

The attorney may attempt to make the witness admit one or more facts or one or more matters of opinion which will tend to corroborate the examiner's theory of the case.

He may attempt to show that there were certain omissions in the testimony of the witness as to the physical condition in issue, the examination by the doctor, the diagnosis, the treatment, or the prognosis.

If the doctor witness is honest, able, and truthful, he has nothing to fear from any such lines of inquiry. The things for which he should be on the watch are as follows:

1. Confusing questions, i.e., questions that are indefinite and uncertain, double questions, questions that assume the truth of a fact not yet proved.

For example, a question, "If the car were traveling partly in the right lane and partly in the middle lane of the three car highway, how much space would that leave for the cars to pass?" would be indefinite and uncertain. It could not be answered without knowing (a) on which side the other car was to pass, (b) how far into the middle lane the first car was traveling.

A question, "Was the wind from the northeast and of gale strength?" would be a double question, two questions in one. "Was the wind from the northeast?" "Was it of gale strength?" The questions should be separated before the witness should be called upon to answer.

The question, "What part of the plaintiff's body were you examining when you found indications of the former injury?" may be objectionable as assuming a fact not yet proved, viz., that you, the witness, had found in the patient indications of a former injury.

The attorney who called the witness to the stand should be on the lookout to see whether a cross-examiner's question is confusing and to object thereto. If he is neglectful of his duty in this respect the witness should say, "I cannot answer that question."

Question: "Why not?"

Answer: "It is indefinite and uncertain," or "It is two questions in one," or "It assumes that I did find indications of a former injury and that is not the case." The judge will then compel the cross-examiner to reframe the question.

2. The next thing for which the cross-examined witness should be on the watch is some former opinion on a medical question given by the witness which is not in accordance with the theory on which he now testifies. The opinion may be in a book written by the witness or in an article by him in a medical journal. It may be some testimony that he gave years ago as a medical expert in another law suit. If the opinion that was given at the former time was then believed to be the truth but the witness has since changed his mind, he should not hesitate to so state, "Yes, I wrote the article referred to. It was my opinion at the time. I have since changed my opinion on that point and if I were to rewrite that article (if the witness did rewrite the article and can cite the new article to the court he will have scored a triumph) I would report that change in my views." The cross-examiner will doubtless then ask, "What caused you to change your views?" (If the cross-examiner does not ask that question the attorney who called the witness should take pains to ask it on his redirect examination.) Answer: "Further study and experience by me in that class of cases and the writings and researches by others along the same line."

3. A third line of attack for which the witness should be prepared is an attempted trick of a cross-examiner to persuade the witness to cite, as the basis for his opinion, an authority who never existed or an alleged statement by an authority who did exist but who never made the statement claimed. For example, after the cross-examiner has had the witness give the names of certain authorities supporting his theory, he may ask (often with a pile of what look like medical books on the table in front of him):

Question: "Are you acquainted with the writings of Dr. \_\_\_\_\_?"

Answer: "Yes."

Question: "Of Dr. \_\_\_\_\_."

Answer: "Yes."

Question: "Of Dr. \_\_\_\_\_."

Answer: "Yes."

naming in his list of writers at least one man who never existed. Or the questioner may refer to a book by an authority who did exist but who never wrote any such book. Or in an extreme case (extreme for it would be perpetrating a fraud on the court), he may attempt to read from a book something which is not there and have the witness agree or disagree with such statement.

Of course there are only two classes of witnesses against whom the above technics might ever prove effective. One would be the vainglorious charlatan who affects a learning that he does not possess. The other would be the inexperienced young doctor with an inferiority complex who is afraid to admit that there is anything that he does not know. The way to meet such a cross-examination is for the witness, when an author's name is stated or a work is stated of which the witness has never heard, frankly to say that he knows of no such author or no such work. If the questioner undertakes to read from a book let the witness ask to see the book.

#### MANNER OF TESTIFYING

What makes one doctor a good witness and another a poor one? The difference is more than in the amount of learning possessed by one or the other or the amount of experience that either has had. It is in the impression he makes on the jury as being earnest, as being an able scientist, and as being able to explain difficult matters to a jury in a manner and in language that they will understand. The following advice can be given to a doctor who desires to be an effective witness.

1. The doctor should be honest with his client and with the court. If the client's injuries are trifling and there is very good certainty of recovery he should be so told. If the sound consensus of medical opinion is against the contentions of the party by whom he is called, he should so tell the attorney calling him and if the attorney persists in placing him on the stand he should so tell the court.

2. The doctor should not undertake to testify as an expert witness unless he feels that he is qualified on that particular subject. If he has spent his whole life in general surgery he should not testify in a will case on problems involving mental diseases, unless he has as a side line interested himself in such problems, any more than the ordinary psychiatrist should testify as to the best method of reducing a Potts fracture.

3. If asked a question that stumps him the doctor should not hesitate to say, "I do not know the answer to that question."

4. The doctor should not be too "cagey" in his replies to questions, for he may give the impression of either not knowing the subject on which he is examined or of not being willing to give his opinion on anything.

5. He should attempt to make a direct answer to every question asked

him. If he thinks a direct answer "Yes" or "No" might be misleading, he should so state to the judge.

6. He should know and remember that he is there to help the court to a better understanding of the problems under consideration and that no matter how hard a cross-examiner presses him he will always have the opportunity to explain his answers to questions. He may say at the time, "I think that I should explain that answer." Generally the judge will let him do so. If not, he can explain it when his redirect examination is conducted by the attorney who first called him to the stand. If this attorney overlooks calling for that explanation the doctor should remind him of his desire to so explain.

7. He should depend on his own knowledge of the questions of science involved. In other words, he should not ordinarily quote from medical books unless the cross-examiner insists on his so doing. The cross-examiner may confront the witness with a quotation from a medical book but if the doctor witness considers that the book is wrong and he is right he should not hesitate to say so.

8. He should take care not to use expressions that will make his testimony seem indefinite, "I think," "My impression is," etc. If he really is in doubt he should say so, otherwise his statements should be firm and direct.

9. If his testimony is to be given in narrative form, following such a question as, "when you first examined the patient what did you find his condition to be?" the story that the witness is to give should be arranged in a logical order that can easily be followed by the jury and should be given without digressions or retracings.

10. He should speak slowly (though not too slowly, for that would bore the jury), audibly and distinctly, turning his face to the jury rather than to the examining counsel and address his testimony to the jury. His words and manner of speaking should be just as if he were explaining in his office the same matter to some layman who was interested in learning just where the truth lay.

11. It is needless to say that the doctor should never argue with counsel, also that he should never lose his temper.

#### TESTIMONY IN MALPRACTICE CASES

There is a rule of evidence (which is really a part of the substantive law of malpractice) that, ordinarily the want of skill or care on the part of the doctor can be proved only by expert witnesses. The reason for the rule is obvious. As the plaintiff's case is based upon the contention that the doctor failed to use proper skill or care, the question of whether proper skill or care was used must be determined by those who know what proper skill or care should be. No doctor should be mulcted in damages just because the patient does not now feel well. Although there may occasionally be a case where the negligence of the doctor was so gross that the court will dispense with this rule, in most cases it will be rigorously applied. The result is



that in a suit for damages for malpractice, no matter how meritorious the cause of action may be, if the plaintiff cannot find a doctor who is willing to testify in his behalf it will be impossible for him to prove his case. Often this will be so. All the doctors in the community, with a feeling of mistaken loyalty, may take the position that they must line up for the defendant whatever the merits of the case may be.

The doctor owes a duty to his fellow practitioners to see that the latter are protected against fake causes of action. On the other hand, where there has been actual and actionable negligence on the part of the doctor, the other members of the profession owe a duty to the cause of justice to see that the victim of the malpractice is properly compensated. Let it be hoped that a sense of justice rather than that of mistaken loyalty will guide the decision of the doctor who is asked to testify in such a case.

#### EXTRA COMPENSATION FOR EXPERT WITNESSES

As was stated earlier in this paper, it is the duty of any person who knows anything about the case, including a doctor who treated a party to the cause, to attend the trial when summoned by a writ of subpoena and for such attendance he is entitled only to the ordinary fees prescribed by statute. When, however, he is called as an expert, not because he knows anything about the facts in this particular case, but because he is needed to advise the court upon a principle of science involved in the case, is he entitled to be paid on a professional rather than on an ordinary witness basis?

This problem has occasioned much discussion in the courts, resulting in a considerable division of authority. The argument is made, on the one hand, that the exaction of the valuable special services of an expert, without other than the ordinary witness' pittance is a hardship that ought not to be imposed. On the other hand, it is argued that the hardship upon the professional man who loses his day's fees of fifty or a hundred or more dollars is no greater relatively than upon the clerk or mechanic who loses his day's earnings of five or ten dollars;—each loses his all for the day. Each owes his duty as a citizen to attend and give his evidence when summoned by the court. The same loss of income would occur to the doctor if he were summoned to be a juror and yet he would never think of demanding extra compensation for his services in that public capacity.

Decisions of the courts of different States will be found holding either way on this question and the legislatures also have stepped into the discussion by enacting statutes on the subject. Some such statutes provide for extra compensation for expert witnesses. Other statutes expressly forbid such payments. If the doctor wishes to stand on his rights in that regard, he must investigate to see what the statutes and decisions are in his particular jurisdiction.<sup>22</sup>

Fortunately, however, there is a practical side to this problem which generally renders a study of statutes and decisions unnecessary. The party

calling an expert witness will generally expect to pay him extra for his services, just as he would expect to pay a workman whom he has caused to be summoned an extra amount equivalent to his "lost time." Why should he make such payments when he can obtain the services of the expert for only the normal witness fee? Is the testimony of the expert witness for sale to the highest bidder? Unfortunately history shows that in some cases the answer to the above question is "Yes." The testimony of some expert witnesses seems to vary in effectiveness in accordance with the size of the fee paid for their appearance. Theoretically, however, the compensation which is paid to an expert witness is not for his services as such, but to reimburse him for what he has lost by giving to a particular case time otherwise available for the remunerative practice of medicine. This, of course, is the same theory on which a doctor bases his charges for traveling to treat a patient in a distant city. Also, what the party desires when he summons an expert is not just the off-hand opinion of the witness given on the stand. He wishes an advance study by the prospective witness of the facts in the particular case and of the problems of science involved in the case. For the time spent by the expert in this advance study the party will expect to pay compensation. Therefore there is no reason ethically why a doctor sought as an expert witness should not inform the party calling him that he expects to be compensated for the time he devotes to performing the duties expected of him. Involved in this problem, however, is the question of the duty of the doctor to appear and testify without charge for an indigent litigant who is without the means to compensate his witness. That is a matter of individual conscience for the doctor himself to decide. If he were the one who treated the party as a patient there is little question that it would be his duty to see the case through by testifying on the patient's behalf. On the other hand, if he has had no professional relations with the party and feels that he is being called only because of his eminence in the profession, he may regard the call as an imposition, unless to decline it might, in his opinion, lead to a miscarriage of justice.

The amount of the compensation demanded should not be more than fair reimbursement for time lost based on the doctor's ordinary scale of fees. A greater charge would subject the doctor to the accusation that he is selling his testimony.<sup>23</sup>

#### IMPROVEMENTS IN THE LAW OF EVIDENCE AS TO EXPERT WITNESSES

It is one of the scandals of the law (as well as a scandal in medicine) that, in a case involving medical testimony a litigant can apparently always (except, as above stated, the plaintiff in a malpractice case) find some medical expert to support his theory of the case and that the testimony of medical experts varies with the necessities of the side by which they are called. That is why, for many years, there has been a strong movement, fostered by experienced judges and by the better class of lawyers, to have it that instead of

experts being called by each side to oppose one another in hostile array, each expert apparently owing a duty to the side by which he was chosen, the experts be selected by the judge, either by agreement of the parties or on his own motion—such experts to owe a duty only to the court, that duty being to determine just where the truth lies as to the rules of the science involved in that particular case and their application to the facts of that case. This movement has resulted in the drafting of the Uniform Expert Testimony Act, a statute prepared by the Commission on Uniform State Laws, which statute it is hoped will eventually be enacted in every jurisdiction.

This act provides that where, in a civil or criminal proceeding, issues arise upon which a court deems that expert evidence is desirable, the court on its own motion, or on request of either party, may appoint one or more experts, not exceeding three on each issue, to testify at the trial. These experts shall make such investigation of the subject matter as they deem necessary and shall make their finding in the form of a written report to the court. In addition to their report the experts may be called to testify by the court or by a party to the cause. The parties themselves may also call experts but must give reasonable notice of the name and address of the expert who is to be called and the jury shall be advised as to what experts were appointed by the parties and which ones were appointed by the court. An expert may be asked to state his inferences, whether they are based on his personal observation or on evidence introduced at the trial and seen or heard by the witness, or on his technical knowledge of the subject, without first stating hypothetically in the question the data on which these inferences are based. The compensation of these experts appointed by the court shall be fixed by the court and shall be paid by the litigants in equal parts to the clerk of the court and thereafter assessed as costs of the suit depending upon which party wins.

The passage of such an act in every state will effect a greatly needed reform in the law of procedure in respect to those numerous cases where medical expert testimony is needed to guide the administration of justice.

#### NOTES

##### 1. New York Civil Practice Act No. 352.

The reader's attention is drawn to the fact that in the Symposium on "Scientific Proof and Relations of Law and Medicine" (1st ser., 1943), Professor Zachariah Chafee, Jr. contributed a paper entitled: "Privileged Communications: Is Justice Served or Obstructed by Closing the Doctor's Mouth on the Witness Stand?" *Yale Law Journal* 52: 607, June, 1943. The author pointed out that seventeen states . . . "seem to preserve the view of the English common law that there is no legal check upon the revelation of medical secrets," so that "On the witness stand, at all events, a doctor in these states must tell all he knows," these states being as follows: Alabama, Connecticut, Delaware, Florida, Georgia, Illinois, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, Rhode Island, South Carolina, Tennessee, Texas, Vermont, and Virginia.

Professor Chafee also lists the states which have passed statutes of various sorts

similar to the New York law, and notes the exceptions to the general prohibition contained in the various enactments, saying: "The ensuing list mentions only the date of the original enactment without regard to subsequent amendments. The statutes vary in their terms, particularly as to waiver of the privilege. The ensuing list mentions only variations of especial medical interest, including the fact of adoption of the Uniform Narcotic Drug Act (U.N.D.A.): Alaska (1913) (except for insanity); Arizona (1913) (U.N.D.A.); Arkansas (1919); California (1872) (except for mental condition and venereal disease); Canal Zone (1934); Colorado (1921); District of Columbia (1919) (U.N.D.A.); Georgia (1935); Hawaii (1925) (U.N.D.A.); Idaho (1919); Indiana (1926); Iowa (1897) (U.N.D.A.); Kansas (1923); Kentucky (1915); Louisiana (1928); Maryland (1935) (U.N.D.A.); Michigan (1915) (except for illegal marriage of persons sexually diseased); Minnesota (1913) (except for bastardy); Mississippi (1906); Missouri (1919) (except for abortion); Montana (1935) (U.N.D.A.); Nebraska (1922) (U.N.D.A.); Nevada (1912) (U.N.D.A.); New Mexico (1929) (U.N.D.A.); New York (1828) (except for narcotic investigations); North Carolina (1919) (allows presiding judge of superior court to compel disclosure when necessary to administration of justice, U.N.D.A.); North Dakota (1913); Ohio (1921) (U.N.D.A.); Oklahoma (1931) (U.N.D.A.); Oregon (1920) (U.N.D.A.); Pennsylvania (1895); Philippine Islands (1901); Puerto Rico (1911) (except for malpractice, U.N.D.A.); South Carolina (1934) (U.N.D.A.); South Dakota (1919) (U.N.D.A.); Utah (1917) (U.N.D.A.); Virgin Islands (1920); Washington (1909); West Virginia (1897) (U.N.D.A.); Wisconsin (1919) (except for lunacy and malpractice, U.N.D.A.); Wyoming (1920) (U.N.D.A.)." Chafee, *id.*, pp. 607-8, f.n. 4.

He points out that . . . "several of the states recognizing the doctor-patient privilege in general have adopted the Uniform Narcotic Drug Act, which provides in sec. 17, par. 2, that "information communicated to a physician in an effort unlawfully to procure a narcotic drug, or unlawfully to procure the administration of any such drug, shall not be deemed a privileged communication." In a supporting footnote, he says: "This statute has been adopted in the following states and territories, of which those starred in the list do not recognize a general doctor-patient privilege: Arizona, District of Columbia, Hawaii, Iowa, Maryland,\* Montana, Nebraska, Nevada, New Mexico, North Carolina, Ohio, Oklahoma, Oregon, Puerto Rico, South Carolina,\* South Dakota, Tennessee,\* Texas,\* Vermont, West Virginia, Wisconsin, Wyoming." Chafee, *id.*, p. 608, f.n. 5.

2. In this respect the New York legislation is unique as rarely will such a statute be found to include nurses.
3. Wigmore, J. H.: *Treatise on Evidence*, ed. 3, Little Brown & Co., Boston, 1940, Vol. VIII, p. 817.
4. *Ibid.*
5. *Id.* at p. 818-9.
6. *Battis v. Chicago, Rock Island & Pacific Ry. Co.*, 124 Iowa 623, 100 N.W. 543 (1904).  
A station agent called the company physician to examine a man who had been ejected from a train. Finding a small wound, the doctor dressed it. Held, he could not testify as to anything that the injured man said to him.
7. Wigmore, J. H.: *loc. cit. supra*, no. 3 at p. 823.
8. *Id.* at p. 824.
9. *Green v. R. Co.*, 171 N. Y. 201, 63 N.E. 958 (1902). Here there was no claim that the information given was in any way necessary for the doctor to prescribe treatment. Situations can be imagined, however, where the story of how an injury occurred would be important in prescribing treatment, e.g., a wound apparently caused by a bite.
10. *Perry v. Hannagan*, 257 Mich. 120, 241 N.W. 233 (1932).
11. Wigmore, J. H.: *loc. cit. supra*, no. 3 at p. 831.

12. Wigmore, J. H.: *loc. cit. supra*, no. 3 at pp. 830-840.
13. *Id.* at p. 840.
14. *Id.* at pp. 808-810.
15. *Id.* Vol. III at pp. 2-4. The author quotes very appropriately from the great dramatist in Pericles, Act III, Sc. 2.

"I ever  
Have studied physic, through which secret art  
By turning over authorities I have—  
Together with my practice—made familiar  
To me and to my aid the blest infusions."

16. *Id.* at p. 8.
17. See again Shakespeare, King John, Act V, Sc. 4.  

"Have I not hideous death within my view,  
Retaining but a quantity of life,  
Which bleeds away, even as a form of wax  
Resolveth from his figure 'gainst the fire?  
What in the world should make me now deceive,  
Since I must lose the use of all deceit?  
Why should I then be false, since it is true  
That I must die here, and live hence by truth?"
18. Schweitzer, S. C.: Trial Manual for Negligence Actions (2nd ed.), New York, Baker, Voorhis & Co., 1941, p. 829.
19. Scott, C. E.: Photographic Evidence, Kansas City, Vernon Law Book Co., 1942, p. 746.
20. *Id.* at pp. 506-514.
21. Goldstein, Irving, and Shabat, L. Willard: Medical trial technique, 1942, Chicago, Callaghan & Co., p. 19.
22. See, in this Symposium series, Goble, George and Smith, Hubert W.: Rights of Compensation for Medical Services.
23. Fee arrangements which are contingent on success of the litigant at whose instance the physician testifies, and agreements for a percentage of the damages recovered, are generally held by the courts to be illegal and so void. The reason is that any fee arrangement which gives the expert witness an interest in seeing one party prevail is inconsistent with his obligations to testify truthfully and impartially as an officer of the court. See Goble and Smith, *id.*

# OBSERVATIONS ON MASS CHEMO-PROPHYLAXIS WITH SULFADIAZINE \*

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It is the purpose of this communication to report an analysis of mass sulfadiazine prophylaxis. About 20,000 soldiers were given the prophylactic medication for a period of five weeks. Perusal of the literature reveals that the prophylactic use of sulfonamides has been investigated and studied by both military and civilian authorities. Thomas and France<sup>1</sup> administered prophylactic sulfanilamide for four years in doses of 1.0 to 1.2 grams a day to a group of rheumatic adolescents and young adults and compared the results with those observed in an untreated control group of similar subjects. Their results showed not a single major attack of rheumatic fever occurred in any patient, nor did any of the patients suffer from any acute beta hemolytic streptococcic infection. In contrast, 15 major rheumatic episodes were observed among the control patients during the same period. Coburn and Moore<sup>2</sup> gave prophylactic sulfanilamide to a group of rheumatic children and observed only one rheumatic recurrence among 184 subjects. Favorable results with prophylactic sulfonamides in preventing rheumatic recurrences have been published by Feldt,<sup>3</sup> Kutner, and Reysersbach,<sup>4</sup> etc. Thomas,<sup>5</sup> in summarizing the literature on rheumatic recurrences, states "that up to present time (October 1944) in civilian life prophylactic sulfanilamide has been administered to rheumatic subjects for a total of 815 patient persons over a period of seven years. Only eight have had recrudescences, an incidence of less than 1 per cent, while the incidence among control groups ranged from 10 to 35 per cent." Investigations conducted during the past two years in the Army by the Army Epidemiological Board and others indicate that the incidence of meningococcal meningitis, of certain streptococcal diseases, and certain upper respiratory diseases of bacterial origin may be markedly reduced by the prophylactic administration of small doses of sulfadiazine.<sup>6</sup> The U. S. Navy's experiment last winter with mass sulfadiazine therapy resulted in an 80 to 90 per cent reduction in hospitalization for severe respiratory diseases, while streptococcic infections were reduced by 85 per cent and meningococcus meningitis practically disappeared.

Sick call records at our seven dispensaries during the first 15 days of January, 1945, revealed an unusually high sick call rate, the majority of patients exhibiting upper respiratory infections characterized by malaise, low grade fever, and red throats. Most of these patients improved with routine therapy and 24 hour rest in quarters. There was also a high percentage

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(23 per cent) of acutely ill patients with high septic temperatures, diffusely injected pharynges, and cervical and submental adenopathy, resembling clinically acute streptococcic sore throat. These were hospitalized. Further, during the four weeks preceding January 15, 1945 we had admitted eight cases of rheumatic fever.

During the eight day period ending January 7, 1945 the average number of daily hospital admissions for respiratory diseases was 9.7, about 7 per cent of which was attributed in origin to streptococci. In the following eight day period this daily average jumped to 37.5. Clinically, about one fourth of the 300 cases admitted during this latter period were of streptococcal origin. During comparable periods in 1944 we averaged 28.4 and 19.6 daily admissions, respectively. It should be noted that the trainee population at this post is almost completely renewed every four to five months. Each week approximately 1000 trainees leave camp and a like number arrive fresh from civilian life. The training cycle of 15 weeks thus represents practically the total military experience of our subjects in this study.

Army regulation<sup>6</sup> authorizes the use of sulfadiazine prophylaxis when the admission rate per 1000 per annum for common respiratory diseases including influenza exceeds 400 for a period of a week or more, provided that more than 20 per cent of the cases can be attributed to the hemolytic streptococcus bacteriologically or clinically. During the period of January 8 through 15, our hospital admission rate per 1000 per annum for common respiratory diseases jumped to 585; therefore, chemoprophylaxis was instituted. Reference to chart 3 reveals that this incidence of respiratory diseases was almost twice as great as during a like period in 1944. It will also be noted that we had had an even greater epidemic in December 1943 and January 1944 and we feared a repetition during the early weeks of 1945, inasmuch as the prevailing epidemiologic factors were essentially unaltered. These facts provided additional incentive for the institution of sulfadiazine prophylaxis.

In this chemoprophylaxis program one gram of sulfadiazine was administered daily to all infantry personnel for a period of five weeks. The soldiers were instructed to report to the dispensary immediately upon the discovery of a rash or any other untoward reactions to the drug, such as sore throat, nausea, vomiting, etc. The dispensary surgeons were likewise advised to be on the alert for toxic manifestations. In addition, the medical officers were directed to notify in writing each reactor's commanding officer, recommending immediate discontinuation of prophylaxis. A duplicate notification with added description of the reaction was to be forwarded to one of us (MSA). Thus, an opportunity was offered to the authors to investigate and study the results of mass sulfadiazine prophylaxis.

*Effect of Prophylaxis on Hospital Admissions.* Chart 1 shows the number of common respiratory diseases hospitalized daily from December 1, 1944 through March 31, 1945. From this chart it is evident that almost all lows occur on Sundays, and a few on Saturdays. It is, of course, a common

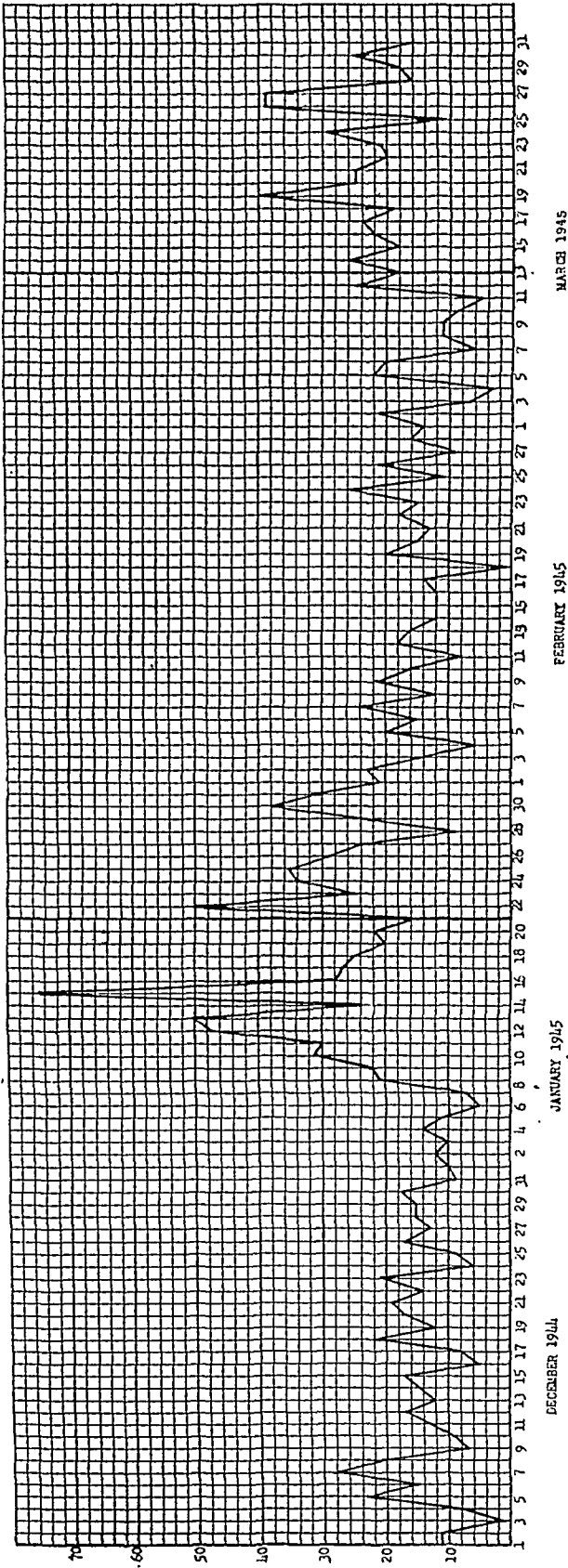


CHART 1. Daily hospital admissions for common respiratory diseases from December 1, 1944 through March 31, 1945.



observation that trainees are loath to report on sick call on Saturday evenings and Sunday mornings. It is, therefore, quite significant that on Sunday, January 14, 1945, twenty-two respiratory cases were hospitalized which, with but one exception, exceeded the admissions for any single day during

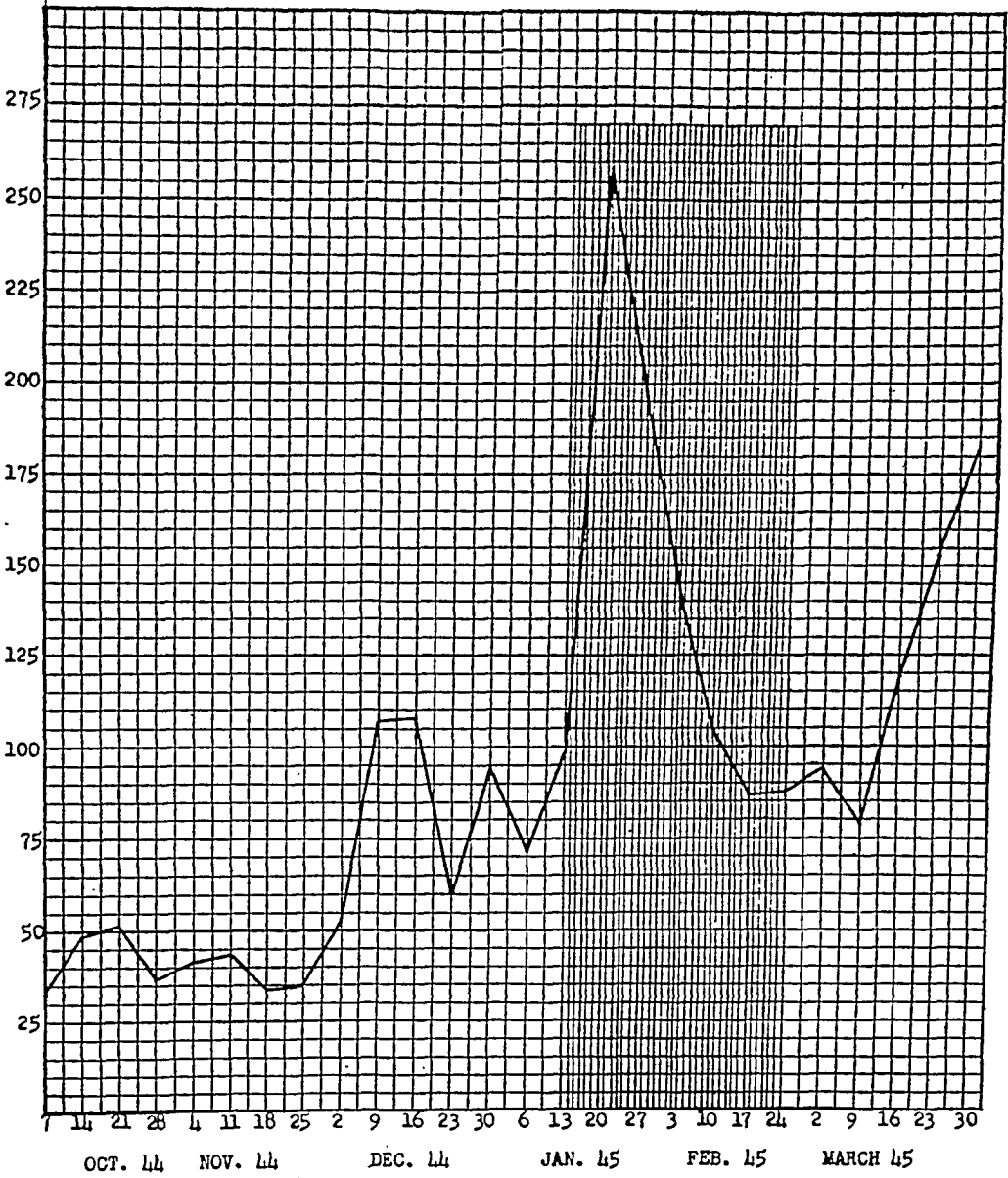


CHART 2. Weekly hospital admissions for common respiratory diseases from week ending October 7, 1944 through week ending March 30, 1945. Shaded area represents period of chemoprophylaxis (January 15, 1945 through February 24, 1945).

the preceding 15 weeks. It is evident, also, that there is a sharp progressive rise during the period January 7-13, then the Sunday recession, and then the peak of 75 cases on January 15. That afternoon mass chemoprophylaxis was begun and the incidence is seen to drop to 28, 27, 25, and 20 on

January 16, 17, 18 and 19, respectively. Sub-peaks are then reached on the following Monday and then on Tuesday of the succeeding week. Thereafter, admissions closely parallel those of the six week period prior to chemoprophylaxis. After discontinuation of prophylaxis on February 24,

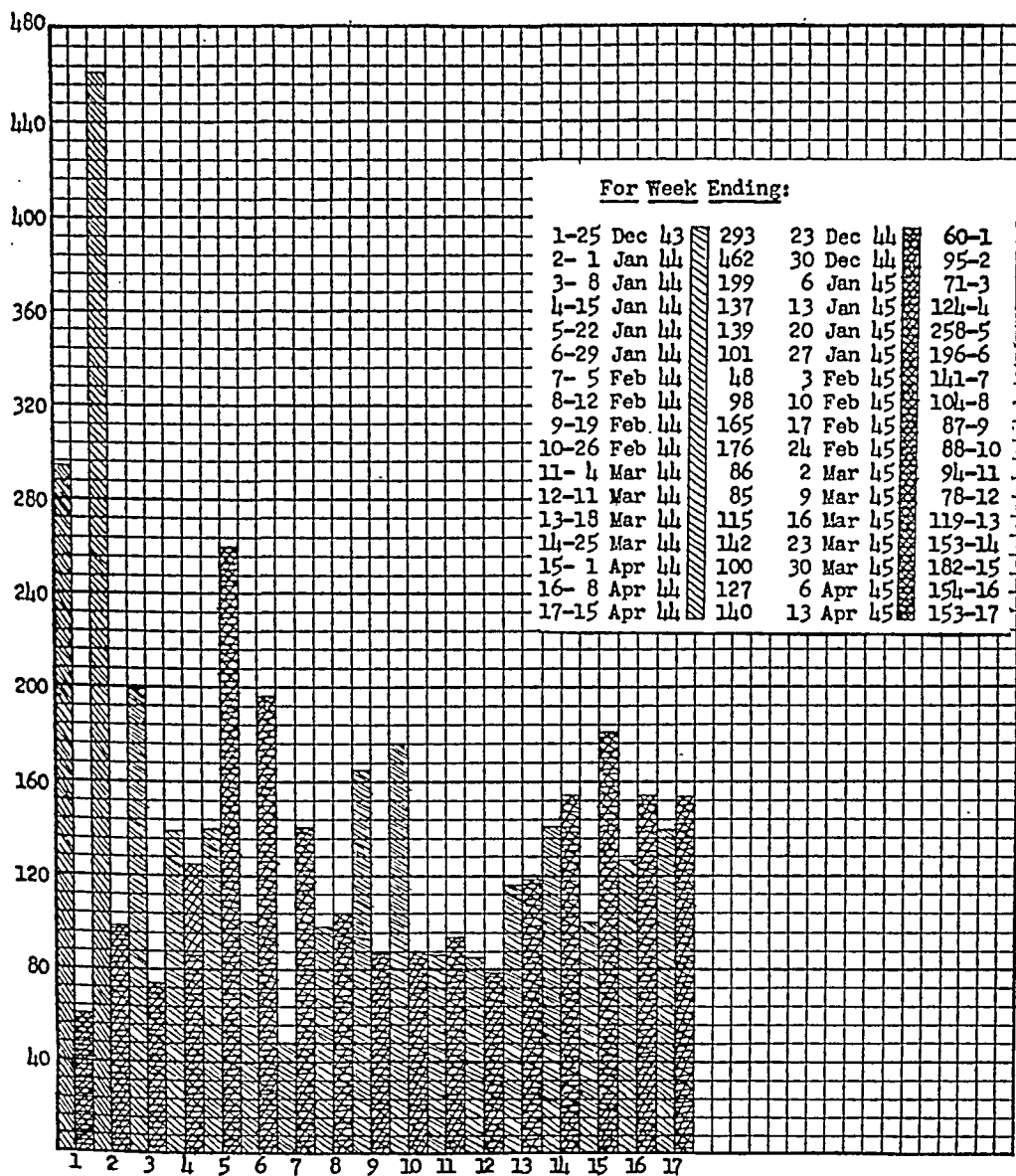


CHART 3. Common respiratory admissions to hospital by weeks in comparable periods of two successive years.

the incidence remains low until March 12, when the curve attains a higher level and continues to ascend.

Projected on a weekly basis, thereby contracting the daily figures of chart 1 sevenfold and absorbing the Saturday and Sunday lows, this respiratory curve is brought into bold relief by chart 2. Chart 2 illustrates the steady decline of respiratories during the period of prophylaxis, the apparent

after-effects of the program, and then the re-acceleration of the rate in March, 1945.

Table 1 contains an analysis of the total admissions to the hospital by weeks broken down into the following disease groups: common respiratory diseases, meningococcic meningitis, rheumatic fever, pneumonia, and scarlet fever. During the period of chemoprophylaxis from January 15 through February 24, no cases of meningitis (meningococcic) occurred. During the

TABLE I  
Weekly Hospital Admissions for Common Respiratory Diseases, Meningitis,  
Rheumatic Fever, Pneumonia and Scarlet Fever  
October 7, 1944 through April 13, 1945

For Week Ending	Common Respiratory Diseases	Meningitis (Meningo- coccic)	Rheumatic Fever	Pneumonia		Scarlet Fever
				Lobar	Atypical	
Oct. 7, '44	33	1	2	0	1	0
Oct. 14, '44	49	0	0	1	1	0
Oct. 21, '44	51	0	2	0	0	0
Oct. 28, '44	37	0	1	0	11	0
Nov. 4, '44	42	0	1	3	4	0
Nov. 11, '44	44	1	2	0	10	0
Nov. 18, '44	34	0	2	0	3	3
Nov. 25, '44	35	0	1	1	6	1
Dec. 2, '44	53	0	1	0	8	0
Dec. 9, '44	107	0	2	2	10	1
Dec. 16, '44	108	0	0	2	19	2
Dec. 23, '44	60	0	4	1	14	0
Dec. 30, '44	95	0	2	7	9	1
Jan. 6, '45	71	0	1	2	24	0
Jan. 13, '45	124	0	1	1	13	0
Jan. 20, '45	258	0	0	1	24	0
Jan. 27, '45	196	0	1	0	6	0
Feb. 3, '45	141	0	1	2	6	0
Feb. 10, '45	104	0	0	3	8	0
Feb. 17, '45	87	0	1	3	8	2
Feb. 24, '45	88	0	1	2	5	0
Mar. 2, '45	94	0	2	3	10	1
Mar. 9, '45	78	2	1	3	14	0
Mar. 16, '45	119	0	3	6	21	1
Mar. 23, '45	153	0	1	1	22	1
Mar. 30, '45	182	1	2	2	12	0
Apr. 6, '45	154	0	1	2	12	1
Apr. 13, '45	153	2	1	3	18	2

same period there were only four rheumatic fever admissions; whereas during a like period immediately prior to prophylaxis there were 10 such admissions and again 10 admissions during the same interval immediately following cessation of the program (table 1). There was a steady diminution in the number of common respiratory admissions during prophylaxis. Admissions for scarlet fever declined only slightly. Lobar pneumonias declined by approximately one fourth. We are unable to explain the sharp drop in admissions for atypical pneumonia. These facts will be commented upon more fully in the discussion.

TABLE II  
Hospital Admissions for Untoward Sulfadiazine Reactions

Case	Temperature	Rash	Clinical Findings	Laboratory for Throat Culture and White Blood Cell Count	Admission Diagnosis	Progress
1	98.6	Maculopapular generalized	Asymptomatic except for conjunctivitis	Not done	Sulfadiazine rash	Immediate remission
2	99.2	Scattered maculopapular on face	Post-cervical adenopathy itching	W.b.c. 4000—polys. 57, lymphs. 37, monos. 4	Obvn. German measles	Immediate remission
Arriving at barracks given 1 gm. of sulfadiazine—within 2 hours began to feel sick and was re-admitted with:						
	102.8	Generalized maculopapular	Malaise	Not done	Sulfadiazine rash	Remission in 24 hours
3	98.6	Maculopapular on back, face, trunk	Edema of wrists and face, pharynx-injected	W.b.c. 8800—polys. 43, lymphs. 40, monos. 9, eosinophiles 8	Sulfadiazine rash	Remission in 12 hours
4	102.6	Maculopapular generalized	Pharynx-injected	W.b.c. 4600, polys. 59, lymphs. 32, eos. 3	Sulfadiazine rash	Remission in 24 hours
5	101.4	Maculopapular on back, trunk, hands and knees	Pharynx-injected, malaise	W.b.c. 10,200, polys. 67, lymphs. 21, monos. 7, eos. 5	Sulfadiazine rash	Febrile for 4 days
6	98.6	Faint erythematous flush, generalized	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission
7	102	Confluent erythematous flush over back and trunk and face	Acute rhinitis Pharynx-injected	Not done	Acute nasopharyngitis	Remission in 24 hours
Back at barracks given 1 gm. sulfadiazine, fainted within an hour and admitted with:						
	102.8	Maculopapular generalized	Malaise	W.b.c. 5100, polys. 53, lymphs. 42, monos. 4	Sulfadiazine rash	Remission in 24 hours

TABLE II—Continued

Case	Temperature	Rash	Clinical Findings	Laboratory for Throat Culture and White Blood Cell Count	Admission Diagnosis	Progress
8	102.8	Faint erythematous flush on face and trunk	Malaise	Not done	Sulfadiazine rash	Remission in 12 hours
9	102	Confluent erythematous over trunk	Post-cervical adenopathy headache, pharynx-injected, acute rhinitis	Not done	Acute nasopharyngitis	Immediate remission
Arriving at barracks took 1 gm. of sulfadiazine—became ill shortly after with:						
	102.8	Generalized scarlatiniform	Malaise, nausea	W.b.c. 6500, polys. 67, lymphs. 25, monos. 5, eos. 2	Sulfadiazine rash	Remission in 24 hours
10	98.6	Maculopapular on both forearms and groins	None	Not done	Sulfadiazine rash	Immediate remission
11	100.2	Scarlatiniform on thorax and arms	Pharynx-injected, headache, chest pain	Throat culture negative for Beta hemolytic streptococci. W.b.c. 6700, polys. 74, lymphs. 18, monos. 5, eos. 3	Obvn. for scarlet fever	Remission in 24 hours
12	100	Scarlatiniform generalized	Pharynx-injected, malaise, strawberry tongue, axillary adenopathy	Throat culture negative for Beta hemolytic streptococci. W.b.c. 8700, polys. 82, lymphs. 11, monos. 1, eos. 2	Obvn. for scarlet fever	Remission in 24 hours
13	102	Scarlatiniform on thorax	Pharynx-injected, headache	Throat culture negative. W.b.c. 4900, polys. 6, lymphs. 32, monos. 32, eos. 3	Obvn. for scarlet fever	Remission in 24 hours
14	98.6	Maculopapular over trunk and arm	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission

TABLE II—Continued

Case	Temperature	Rash	Clinical Findings	Laboratory for Throat Culture and White Blood Cell Count	Admission Diagnosis	Progress
15	99.6	Discrete maculopapular over chest	Pharynx-injected	Not done	Sulfadiazine rash	Remission in 24 hours
16	104	Erythematous punctate over trunk	Generalized lymphadenopathy	W.b.c. 9400, polys. 70, lymphs. 22, monos. 6, eos. 2	Sulfadiazine rash	Remission in 48 hours
Hospitalized for 10 days for acute nasopharyngitis—discharged and returned to barracks: given 1 gm. of sulfadiazine—taken ill within 3 hours with:						
17	102.4	Faint erythematous, generalized	Malaise and pain in bones and joints	Not done	Sulfadiazine rash	Remission in 36 hours
18	98.6	Generalized maculopapular	Asymptomatic except for itching	Not done	Sulfadiazine rash	Immediate remission
19	98.6	Fine maculopapular over body	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission
20	98.6	Maculopapular on face and shoulders	Post-cervical adenitis	Not done	Obvn. for German measles	Immediate remission
21	98.6	Maculopapular on face and chest	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission
22	100.2	Brownish erythematous flush, face, trunk, extremities	Post-cervical adenitis, pharynx red	W.b.c. 6800, polys. 69, lymphs. 21, monos. 7	Sulfadiazine rash	Remission in 36 hours

TABLE II—Continued

Case	Temperature	Rash	Clinical Findings	Laboratory for Throat Culture and White Blood Cell Count	Admission Diagnosis	Progress
23	100	Scarlatiniform over chest and back	Asymptomatic	5200, polys. 70, lymphs. 21, monos. 6, eos. 3	Sulfadiazine rash	Remission in 24 hours
24	98.6	Urticaria generalized	Asymptomatic	6400, polys. 64, lymphs. 36	Sulfadiazine rash	Remission in 24 hours
Became ill after 1st dose within 3 hours						
25	101.6	Erythematous flush over body	Malaise	7200, polys. 62, lymphs. 20, monos. 11, eos. 7	Sulfadiazine rash	Remission in 24 hours
26	101	Maculopapular neck, face and chest	Pharynx-injected, post cervical gland	4500, polys. 55, lymphs. 38, monos. 4, eos. 2	Obvn. German measles	Remission in 24 hours
27	102.4	Scarlatiniform generalized	Pharynx-injected	10,000, polys. 91, lymphs. 3, eos. 1, monos. 5	Obvn. scarlet fever	Remission in 48 hours
28	99	Erythematous flush	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission
29	98.6	Maculopapular trunk and upper extremities	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission
30	98.6	Urticaria over chest and trunk	Asymptomatic	Not done	Sulfadiazine rash	Immediate remission

*Reactions to Prophylactic Sulfadiazine.* The untoward reactions to prophylactic administration of sulfadiazine were studied as two groups: those admitted to hospital and those observed and treated as out-patients. Table 2 is a résumé of the 30 cases hospitalized. A glance shows that among the patients five (cases 11, 12, 13, 23, and 27) were admitted for observation for scarlet fever, and three (cases 2, 20 and 26) were admitted for "possible German measles." It was only after negative throat cultures for beta hemolytic streptococci and observation of the clinical progress that these diseases were eliminated. The rashes consisted of maculopapular, faint confluent erythematous, and scarlatiniform eruptions. With the exception of case 16 which showed a temperature of 104° F., the temperature ranged between 99.6° and 102.8° F. All patients except cases 16 and 27 (48 hours) and case 22 (36 hours) became afebrile within six to 24 hours after admission. Eleven patients showed injected and diffuse pharyngitis. Post-cervical adenopathy was present in four patients and one had a generalized lymphadenopathy. Two patients (cases 2 and 26) had a white blood cell count of 4000 and 4500 respectively which is below the accepted level of leukocyte count.<sup>7</sup> Under normal conditions from 2 per cent to 4 per cent of leukocytes found in adult human blood are eosinophiles. Three patients, cases 3, 25 and 5, showed an eosinophilia of 8 per cent, 7 per cent, and 5 per cent respectively.

Among the ambulatory cases, there were 33 patients with mild untoward reactions who were seen and treated by the dispensary surgeons. Table 3

TABLE III  
Ambulatory Patients with Untoward  
Sulfadiazine Reactions

Rash (urticaria, maculopapular, scarlatiniform)	Edema (eyelids, cheeks, wrists)	Gastrointestinal (nausea, vomiting)
22	5	6

is a résumé of these cases. These comprise 22 patients with skin reactions, consisting of urticaria, maculopapular and scarlatiniform rashes; five cases of mild angioneurotic edema involving eyelids, cheeks and wrists; and six cases of gastrointestinal complaints consisting of nausea and vomiting.

#### COMMENT

The following is stated in the Bulletin of the U. S. Army Medical Department<sup>8</sup>: "Chemo-prophylaxis offers a promising means of controlling a group of diseases which always have been a serious threat to military groups, especially recently inducted troops. There is ample reason to believe that it will markedly reduce the morbidity and mortality of these diseases, will diminish interference with training programs on account of sickness and



lessen the incidence of crippling sequelae and complications." Our results with mass sulfadiazine prophylaxis substantiate these statements. At a time when troops are urgently needed for overseas replacement, we have been able to conserve countless man-days necessary for training by cutting the incidence of certain diseases and hospital admissions. During the period of chemoprophylaxis our weekly admission rate for common respiratory disease was reduced by 33 to 59 per cent. It is worthy of comment that we had two meningococcic meningitis admissions within two weeks after cessation of prophylaxis, the subjects being recent inductees who arrived in camp after the program had been concluded. There was a noticeable drop in lobar pneumonias to 11 cases compared with 15 and 17 during like periods before and after prophylaxis, respectively. The drug had slight influence, if any, upon the incidence of scarlet fever (table 1). It would appear, therefore, that sulfadiazine prophylaxis as employed here exerts no appreciable effect on the prevention of this disease. Ratner<sup>8</sup> frowns upon the therapeutic use of sulfonamides in scarlet fever and quotes numerous observers who doubt the efficacy of the drug in lowering the incidence of complications of this disease. Our study reveals a sharp drop (36 per cent) in the number of atypical pneumonias admitted to hospital during the program. It is difficult to comprehend the reason for this drop. Both chemotherapy and serotherapy have been found to have no influence upon virus disease. Conjecture upon the factors underlying the diminished incidence of atypical pneumonia is not within the scope of this paper; nevertheless, it may not be amiss to suggest further investigation along these lines. Our results showed a marked diminution in rheumatic fever episodes during chemoprophylaxis, admissions having been cut by 60 per cent. It must, of course, be borne in mind that all soldiers in this program (except those hospitalized) remained on a full duty status. The duties of an infantry trainee at this Infantry Replacement Training Center are rigorous indeed and certainly conducive to recurrences of rheumatic episodes in diathetic individuals. It may be assumed, therefore, that the incidence of rheumatic fever would have been diminished even farther if we had been able to limit the activities of individuals with rheumatic histories.

Analysis of our untoward reactions from mass sulfadiazine prophylaxis reveals the figure to be very low. There were no serious reactions. Among approximately 20,000 individuals taking a daily one gram dose of sulfadiazine for a period of five weeks there were 63 who reacted adversely. Thirty of these were admitted to the hospital for further study and treatment; the remaining 33 were treated at the dispensaries.

It is interesting to note that among the 30 hospital cases, five had an admission diagnosis of "observation scarlet fever," and three were admitted for "observation German measles." The similarity between the reaction due to sulfadiazine and the symptoms of early scarlet fever and German measles is such that sometimes only after appropriate laboratory tests and clinical progress could the correct diagnosis be established. Therefore, one must ques-

tion patients whether they have recently received sulfonamide drugs when faced with apparent acute exanthematous infections. Skin eruptions were present in 52 of all reactors, while 30 had pyrexia and rash. Sore throat and malaise were common symptoms.

It is not within the scope of this paper to enter into a detailed discussion concerning the mechanism of sulfonamide reaction. There is no doubt that primary toxic reactions do occur after sulfonamide therapy, particularly when given in large amounts. Ratner<sup>8</sup> stresses that up to the present time all aberrant reactions to these drugs have generally been classed together indiscriminately under the designation of "toxic reactions." He points out that as these drugs are used for prophylaxis and therapy repeatedly in a wide variety of diseases untoward reactions will occur which are not toxic reactions but rather the development of hypersensitivity to the drug. A careful study of our cases seems to verify Ratner's hypothesis. One of us (BWB) personally interrogated more than one-half of the reactors.<sup>36</sup> Fourteen among them stated that they had taken at one time or another some form of "sulfa drugs" with impunity. Six others thought they were given sulfa tablets by their physicians for colds, but were not certain; the rest professed ignorance about having taken the drug before. Among the reactors several developed a reaction comparable to serum sickness, i.e., an incubation period of six to 14 days after beginning prophylaxis, an abrupt febrile onset, malaise, rash, itching and nausea and eosinophilia. Others on the other hand reacted immediately upon taking the drug, resembling the so-called accelerated type of serum allergy. The case history of patient 2 may be cited as an example. The patient had been receiving prophylactic sulfadiazine for about 12 days when he developed a scattered maculopapular eruption of the face, itching, and posterior cervical adenopathy. He was afebrile and was admitted with a diagnosis of observation for German measles. He improved rapidly and after four days was discharged. Arriving at his barracks he was given 1 gram of sulfadiazine. Within two hours he began to feel sick, developed generalized maculopapular rash with a temperature of 102.8° F., and was readmitted, this time with the proper diagnosis. Cases 7, 9, 17, 25 and 27 present similar histories. One may further conclude that the repetition of sulfadiazine even in small doses in a previous reactor to the drug may precipitate an immediate untoward reaction.

#### SUMMARY

1. Mass sulfadiazine prophylaxis was instituted for a period of five weeks after hospital admissions for common respiratory diseases reached an alarmingly high rate with 23 per cent due to hemolytic streptococci clinically.
2. One gram of sulfadiazine was administered daily to about 20,000 soldiers.
3. During chemoprophylaxis our hospital admission for common respiratory diseases dropped by 33 per cent at the end of the first week.

4. There were no cases of meningitis during the period of prophylaxis whereas there were two admissions within the following two week period.

5. There was a marked diminution of episodes of rheumatic fever during sulfadiazine prophylaxis.

6. There was a noticeable drop in lobar pneumonias during the program.

7. There was a drop of about one-third in admissions for atypical pneumonia. We do not know whether this finding was coincidental or related to our program.

8. Sulfadiazine prophylaxis did not appreciably influence the incidence of scarlet fever.

9. There were no serious reactions to the drug. However, among the total of 63 reactions, 30 were admitted to the hospital for further study. Thirty-three were observed and treated as out-patients.

10. Among the 30 hospital cases, five were admitted with a tentative diagnosis of scarlet fever and three of German measles. It was only after negative throat cultures and observation of clinical progress that these diseases were eliminated. All hospitalized patients had fever of short duration and skin eruptions.

11. Among the 33 ambulatory cases, there were 22 patients with skin reactions consisting of urticaria, maculopapular, and scarlatiniform eruptions; five with mild angioneurotic edema; and six cases of gastrointestinal complaints consisting of nausea and vomiting.

12. We feel that at least in some instances reactions analogous to allergic sensitizations occurred, manifested by urticaria, angioneurotic edema, and gastrointestinal symptoms. Ratner's hypothesis that reactions are manifestations of sensitization as apart from toxic phenomena is discussed and evidence is offered to support this view. We offer a classic example in case 2 discussed above. We caution against administration of sulfadiazine even in small doses in the presence of a history of previous reactions.

13. In military establishments where troop population is constantly augmented by men fresh from civilian life, routine administration of sulfadiazine prophylaxis appears to be a potent means of reducing non-effective rates. By diminishing the incidence of certain diseases, thereby reducing time lost from training, chemoprophylaxis makes a significant contribution to the winning of the war. Its similar and timely application in civilian life, especially in institutions such as schools, camps, asylums, etc., is fully as promising in reducing the incidence of certain diseases and their sequelae.

14. We are stimulated to further study of reactions to this drug.

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## PEPTIC ULCER IN IDENTICAL TWINS \*

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THE literature concerning the familial incidence of peptic ulcer was reviewed in this Journal in 1933,<sup>1</sup> and although the reports suggested an inherited factor prominent in the basic causes of peptic ulcer, I was unable at the time to find the disease in identical twins or any reference to it in the literature. Since 1933, three instances have appeared in the literature. I wish to report the fourth instance of the occurrence of this pathological process in identical twins as further evidence in support of the hereditary nature of peptic ulcer.

It is rational, in view of the limitation of our present knowledge, to assume that gastric and duodenal ulcers are fundamentally the same disease. In this paper the term *peptic ulcer* refers to the lesion in either location.

In 1935, E. Schindler<sup>2</sup> reported a study of 39-year-old twin brothers who had ulcers of the lesser curvature of the stomach perforating within one month of each other. The diagnoses were confirmed by operation. The family history of these twins contained instances of both cancer of the stomach and peptic ulcer.

In the same year, F. von Mentzingen<sup>3</sup> reported cases of 20-year-old identical twin sisters with roentgenographic evidence of duodenal ulcer, the father of these twins having had a gastroenterostomy for pyloric obstruction.

In 1944, McHardy and Browne<sup>4</sup> reported duodenal ulcer concomitant in identical male twins, aged 28. This report does not include a family history.

In 1938, C. W. Kidd<sup>5</sup> reported similar symmetrical and simultaneous duodenal ulcers in dizygotic male twins, which perforated within an hour of each other. The diagnoses were confirmed by operation. Since these were not identical, the report cannot be used to substantiate our thesis because peptic ulcer in siblings is strikingly common, although to have the accident of perforation occur in each within an hour is an unusual coincidence.

In three of these instances then the peptic ulcers occurred in homologous twins; in the fourth they occurred in dizygotic twins.

The occurrence of cancer of the stomach in these families with peptic ulcer, as mentioned in one of the reports above, is between four and six times as great as in families in which ulcer does not occur, so that it is not surprising that Militzer<sup>6</sup> was able to report in 1935 the occurrence in 70-year-old male twins of symmetrically located cancers of the stomach, with simultaneous, identical symptoms and similar lesions. This instance of cancer of the stomach in twins does not necessarily support the commonly accepted

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theory that gastric ulcers may be precancerous lesions but it does add interest to genetic relationships of the two gastric lesions.

#### CASE REPORTS

An identical twin (Margaret), aged 20, complained of a gnawing sensation in the epigastrium after meals and awakening her at night. Food gave relief. The symptom usually was more pronounced in the spring with relief during the summer and winter. There had been no vomiting and no tarry stools. The symptoms appeared about four weeks after the birth of her first child, when she was 18 years old.

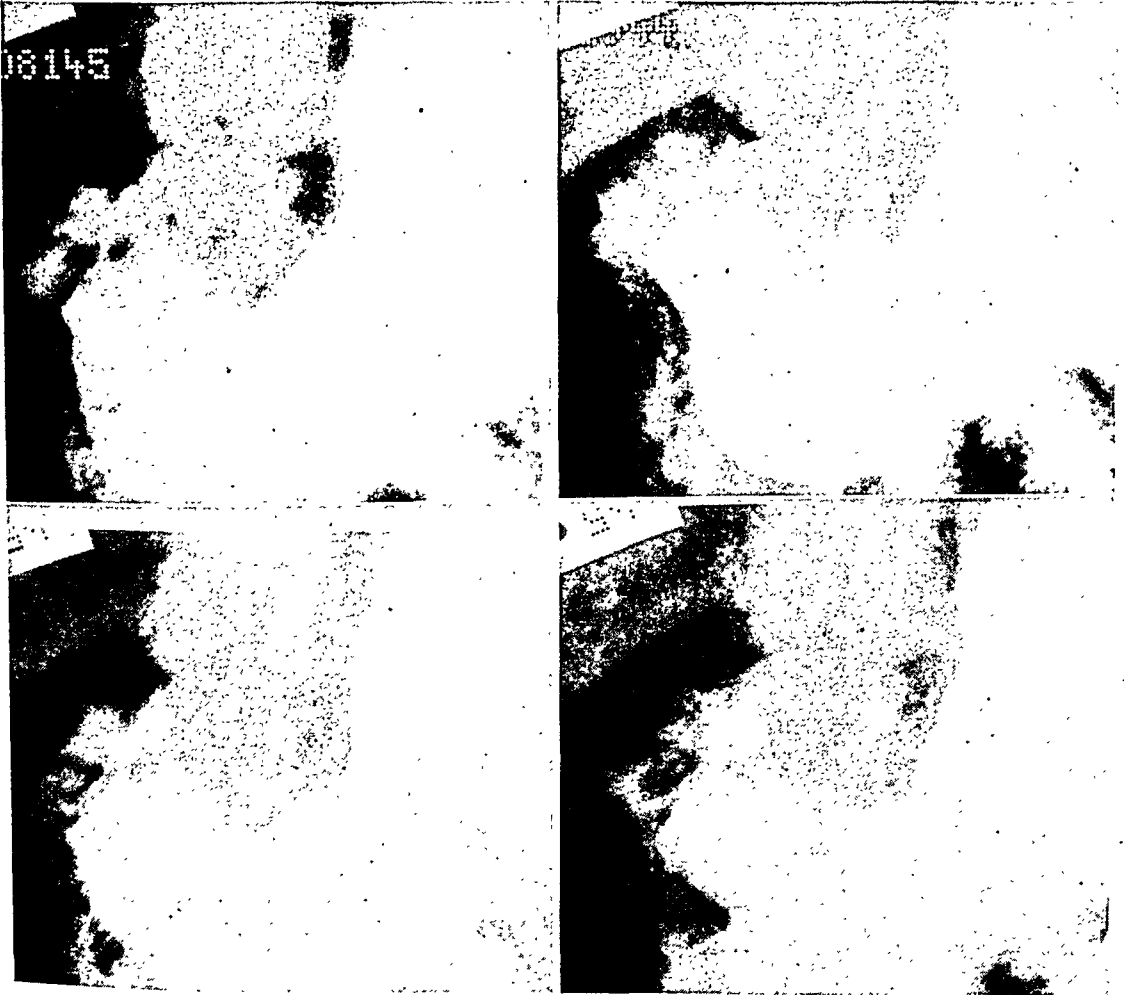


FIG. 1. (Margaret) Showing ragged irregular appearance of the cap in the postero-anterior and lateral projections.

Roentgen studies by Dr. S. M. Donaldson showed an irregular, ragged appearance of the duodenal cap in the posterior-anterior and in the lateral projection (figure 1). A diagnosis of chronic duodenal ulcer was made.

The other twin (Marian) had epigastric distress four months after the birth of her second baby, the first having been stillborn about two years before. Her symptoms were similar to those of Margaret. The roentgenographic studies by Dr. G. T.

Patrick showed extreme tenderness on pressure over the duodenal cap, a marked irregularity of the cap, and a diagnosis of chronic duodenal ulcer was made (figure 2).

The father of these twins had stomach trouble for a number of years and in 1938 a gastric resection for duodenal ulcer was made at the University of Michigan Hospital. The roentgen and clinical evidence in the father's case was unequivocal.

The characterology of these twins follows that consistent in peptic ulcer cases, in that it emphasizes the extreme meticulousness, scrupulousness, and

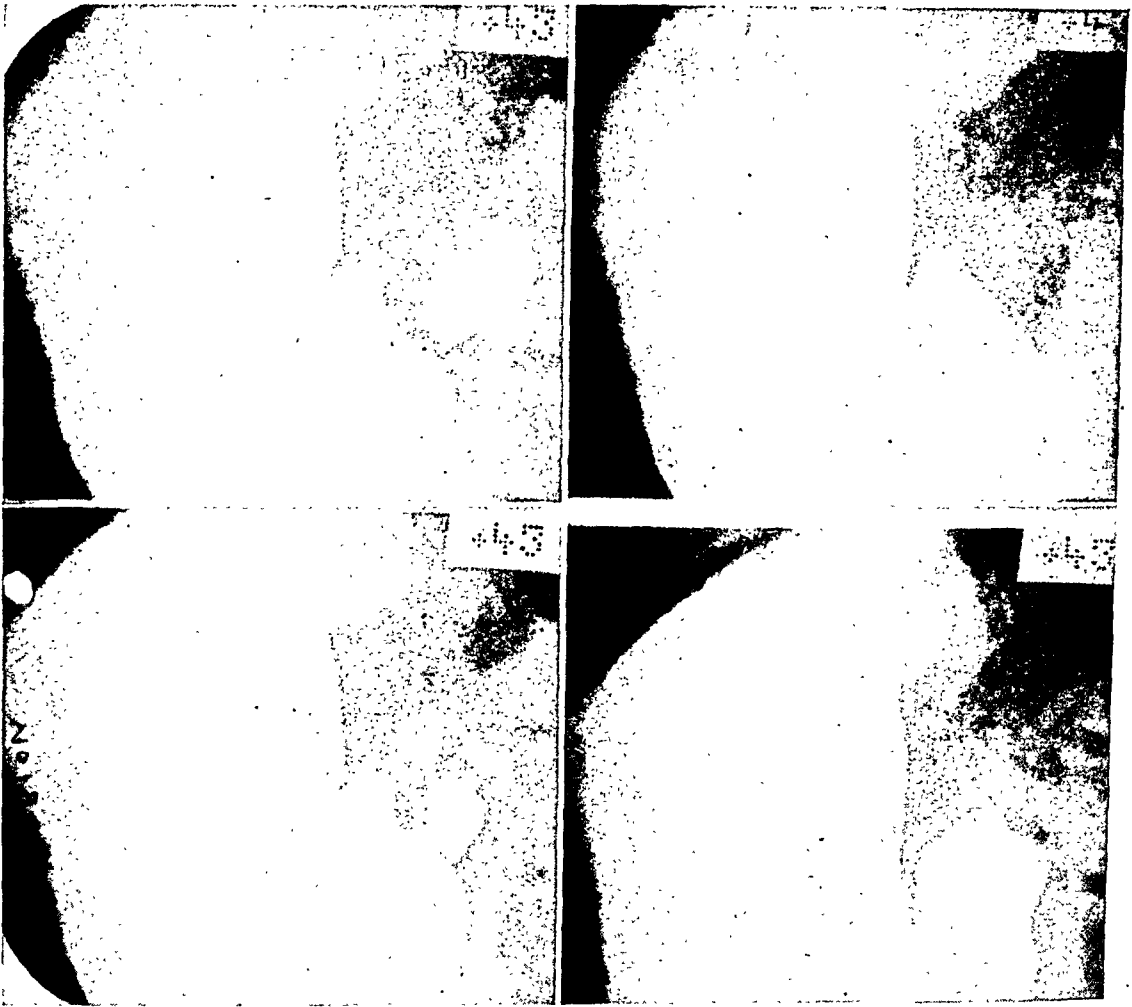


FIG. 2. (Marian) Showing no definite complete filling of the duodenal bulb. The irregularity confirms that noted by the fluoroscope.

neatness of the patients, and their inability to tolerate "disorderliness," all of which is typical of the personality pattern of the ulcer patient. Activation of an ulcer, sometimes with hemorrhage or perforation, occurs when unusual psychic tension referable to these personality characteristics is experienced.

*The Identity of Twins.* There is always some difficulty in determining whether or not twins are homozygotic. Identity of sexes is not sufficient proof. According to the mother's statement there was only one placenta

at the birth of the twins, Margaret and Marian. In appearance they were identical as far as the eye could determine. They married brothers. They had attacks of acute appendicitis within 11 days of each other. Their actions, expressions, and mannerisms were identical. Margaret weighed one and one-half ounces more than her sister at birth, and now weighed ten pounds more than her sister. Their menstrual histories were identical. Their blood groups were the same. The deliveries of their babies were uncomplicated. Their blood pressures were identical.

We attempted to substantiate further the identity by fingerprints and electrocardiograms. The fingerprints were referred to Lieutenant H. E. Ericson, of the Michigan State Bureau of Identification of the Michigan State Police Department, with the following note:

"The fingerprint classification of these prints indicates that there are no similarities between these prints of twins. There is nothing unusual about either set of prints. Numerous sets of prints of twins have been received in the past and occasionally there are similar characteristics but in this case there is nothing which might indicate that they were fingerprints of twins. The following is the fingerprint classification in each case.

Margaret	(19)	L	9	R	O	18
		S	1	Ua	aO	10
Marian	(18)	L	1	A	OO	5
		M	1	U	OI	14"

Since the literature commonly states that identical twins have either identical or "mirror image" fingerprints, this note should be of some interest.

It has been suggested that the electrocardiograms are identical in twins, but Wise, Comeau, and White,<sup>7</sup> among others, found that electrocardiograms are not necessarily similar in identical twins. Electroencephalograms and Rorschach tests were not obtained on these subjects, nor was the phenylthiocarbamide test used.

In the case of Margaret and Marian, the evidence of identity will have to rest upon the similarity of their physical and mental characteristics and the statement of the mother that there was a single placenta at birth.

## DISCUSSION

The observation of the occurrence of ulcer in identical twins introduces several questions. One must agree that the tendency to ulcer is inherited. The mechanism will be understood only after a complete genetic study of all the members of several generations. Do not these patients really inherit a personality type which activates predisposed but unknown components of the autonomic nervous system thus producing hyperchlorhydria or ulcer or both when under emotional tension? A similar situation certainly exists in many other hereditary diseases in that of all the detectable factors making up an inherited clinical entity, some members of the family may show only one or two. We may assume then, that the three most constant factors constituting the clinical entity of peptic ulcer may not appear in all members of a given ulcer family. It is, of course, possible that the hyperchlorhydria accompanying duodenal ulcer may be familial, may be incidental or secon-



dary, and may or may not be related to personality types. It is also possible that separate genes are required for the inheritance of hyperchlorhydria and the personality type, and that the combination in the same person would give rise to the susceptibility to ulcer.

There can be no doubt that peptic ulcer is a familial disease. The evidence for a hereditary component is overwhelming. Both prevention and treatment, if successful, will depend upon a correct evaluation of an inherited personality pattern upon which psychic trauma causes ulcer formation by mediation through known reflex arcs between cerebrum, hypothalamus, and vagus nerve, and the gastric and duodenal mucosa.

It is obvious that the *basic* cause of peptic ulcer is not related to environmental, hormonal, or nutritional factors, although the cholinergic components may be secondarily involved. In this respect interest is being shown in the appearance of coronary thrombosis and peptic ulcer in the same person. Three such instances accurately diagnosed have come to my attention and in one the autopsy showed both lesions to be recent. Coronary thrombosis also occurs in families and reports of the disease are likely to appear concerning identical twins. Both diseases have strong emotional components, both are produced experimentally by vagal stimulation and in animals dying of adrenal insufficiency.

It will be necessary to leave the final answer to these questions to the development of experimental medicine and psychiatry.

#### SUMMARY

Cases of duodenal ulcer in identical female twins are reported. This is the fourth instance of its kind reported in the current literature and further confirms the basically hereditary nature of peptic ulcer.

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## DIPHTHERIA CARRIERS TREATED WITH PENICILLIN \*

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THE majority of patients with diphtheria rid themselves of bacilli within the first two weeks after recovery. However, there remains a fairly large percentage of cases who become carriers and who present a serious danger to the spread of the disease unless isolated or freed of the infecting organism. Heretofore, although a great variety of bactericidal agents has been tried, the treatment of carriers has remained unsatisfactory.

It has previously been shown by Abraham, Chain, et al.<sup>1</sup> Chain, Florey et al.,<sup>2</sup> and by Fleming,<sup>3</sup> that *Corynebacterium diphtheriae* is susceptible to the action of penicillin in vitro. Because of this fact, and because of the large number of diphtheria carriers encountered on our service in one of the army general hospitals, Colonel William S. Middleton, Chief Consultant in Medicine for the ETOUSA suggested that we try the use of penicillin to solve this problem.

### EXPERIMENTAL DATA

1. *Laboratory Studies.* The carrier state was judged by the results of examination of smears taken from cultures grown on tellurite medium. Swabs from the throat and from the nasal mucous membranes were cultured on selected potassium tellurite media, and typical black colonies were fished and confirmed microscopically by stained films. Cultures on tellurite media frequently yield short bacilli with typical granules. Any questionable cases were subcultured on Loeffler's media which yields a more typical organism for microscopic study. Albert's staining technic was used in the diagnostic slide procedure.

As pointed out by Helen A. Wright,<sup>4</sup> positive results from throat cultures may be misleading because "the biological distinction between *Corynebacterium diphtheriae* and related non-pathogenic species is not always sharp." Due to lack of facilities at this hospital, virulence studies were not carried out.

Five consecutive negative nose and throat cultures served as our criteria for release from isolation.

2. *Systemic Treatment.* Nine patients who had recovered from clinical diphtheria and continued to show positive throat cultures for from two to seven weeks after symptoms had subsided were given intramuscular injections of 25,000 units of penicillin every two hours for seven days, for a

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total of 2,100,000 units. As may be seen from table 1 (first five cases) and table 2 (four cases), cultures remained positive in all nine cases treated.

3. *Local Treatment with Penicillin.* The failure of systemic treatment with penicillin becomes understandable when we stop to consider the nature of the diphtheria bacillus. It is well known that this organism has but slight capacity to invade the body and it is found almost exclusively on the surface

TABLE I  
Penicillin Therapy for Diphtheria Bacillus Carriers  
Systemic and Local Treatment

Case No.	Days from Onset	TABLE I																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
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+ = Pos. Culture      - = Neg. Culture      C = Contaminated  
 ~~~~~ = Penicillin 25000 u. intramuscularly every 2 hours. Total 2,100,000 units.  
 — = Penicillin lozenges, 500 u. each, one every hr plus nasal spray of 500 u. per cc every 2 hrs.  
 — = Penicillin lozenges, 1000 u. each, one every hr plus nasal spray 1000 u. per cc every 2 hrs.  
 T = Tonsillectomy  
 — = Penicillin lozenges alone.

TABLE II  
Penicillin Therapy for Diphtheria Bacillus Carriers  
System Treatment Only

| Case No.<br>Days from<br>Onset |    | TABLE II<br>Penicillin Therapy for Diphtheria Bacillus Carriers<br>System Treatment Only |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
|--------------------------------|----|------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|
|                                |    | 1                                                                                        | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |   |
| 33                             | 37 | +                                                                                        | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| 33                             | 56 | +                                                                                        | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| 34                             | 37 | +                                                                                        | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| 35                             | 37 | +                                                                                        | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |

+ = Pos. Culture      - = Neg. Culture  
 ~~~~~ = Penicillin 25000 units intramuscularly every 2 hours. Total 2,100,000 units  
 ~~~~ = Penicillin 40000 units intramuscularly every 3 hours. Total 960,000 units

of the affected mucous membranes. The symptoms and harm produced by the disease are due entirely to the soluble toxin absorbed from the surface of the membranes affected. It would, therefore, seem logical to try the effect of topical application of the bacteriostatic agent. However, penicillin, to be effective, requires more than momentary contact, such as would be produced by painting the surface or by the use of infrequent sprays. In a personal communication from Professor Sir Alexander Fleming, the use of mouth lozenges was suggested. With a little experimentation, our pharma-

cist devised a glycerine and gelatin lozenge that required 20 to 30 minutes to dissolve, when held between the cheek and gums, thus giving prolonged contact with the throat by the released penicillin (formula given below).

Base Presently Used for Penicillin Lozenge:

|                     |               |
|---------------------|---------------|
| Agar                | 30.0 Gm.      |
| Water               | 500.0 c.c.    |
| Glycerite of Starch | 350.0 Gm.     |
| Sucrose             | 720.0 Gm.     |
| Penicillin          | 400,000 units |
| To make             | 400 Lozenges. |

Alternate Base:  
Glycerinated Gelatin

|            |                     |
|------------|---------------------|
| Gelatin    | 800.0 Gm.           |
| Glycerin   | 640.0 c.c.          |
| Water      | q.s. to wet Gelatin |
| Penicillin | 400,000 units       |
| To make    | 400 Lozenges.       |

A total of 31 diphtheria carriers was treated with penicillin lozenges. Each patient received one lozenge every hour for 12 doses during waking hours over a period ranging from three to 15 days. The first patients treated received 500 units per lozenge; after January 1, 1000 units per lozenge was used. Because of the possibility that the nasal mucous membranes also might harbor bacilli, penicillin sprays containing 1000 units per c.c. were given, every two hours, during the same period. Results are shown in table 1.

### DISCUSSION OF RESULTS

Of the 31 diphtheria carriers treated with the lozenges and penicillin nasal spray, 23 or 74 per cent cleared promptly, the cultures becoming consistently negative from the first to the tenth day after beginning treatment. The eight cases in this series that remained positive despite treatment were found to have enlarged cryptic tonsils. We then had these eight patients' tonsils removed, following which seven gave consistently negative cultures without further treatment. When penicillin lozenges and nasal spray treatment were then applied to this one exception over a period of eight days, the cultures from the nose and throat became free from the infecting organisms.

Case 30 was treated at first with the lozenges alone, for a period of 13 days, without success in clearing both the throat and nasal secretions; however, when nasal spray was added to this treatment, they cleared promptly.

The fact that cultures became negative only after tonsillectomy in seven of the cases is considered proof that the tonsils are important sites for harboring diphtheria bacilli. That the nasal passages also may serve as the focus was evidenced by two cases. In one case (No. 31), nasal cultures remained positive after tonsillectomy. In the other (case No. 30), cultures became negative only after nasal spray treatment was added to lozenges.

## SUMMARY

1. Treatment of diphtheria carriers by intramuscular injections of penicillin in adequate dosage over a period of seven days was found to be ineffectual in ridding patients of the diphtheria bacillus.

2. Penicillin lozenges containing 500 and 1000 units per lozenge, taken by mouth, in combination with a nasal spray containing 1000 units per c.c., resulted in five consecutive daily negative cultures in 23 out of 31, or 74 per cent of carriers treated.

3. Eight cases who failed to clear with this treatment alone promptly became negative after tonsillectomy without further penicillin treatment, with one exception. This case cleared readily when again treated with the lozenges and spray.

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# HYPOGLYCEMIA IN NEUROPSYCHIATRY \*

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## INTRODUCTION

THE neuropsychiatric manifestations of hypoglycemia have been described in the literature. Duncan<sup>1</sup> reported the case of a 19-year old girl who complained of attacks of vertigo and headaches. There had been spells of weakness and one morning she became emotionally upset and lost consciousness. A pancreatic adenoma was removed at operation, this having been a case of organic hyperinsulinism.

Conn,<sup>2</sup> in his excellent monograph on the spontaneous hypoglycemias, reported a case of multiple pancreatic islet cell adenomata, the manifestations having been an "aura" of epigastric discomfort and numbness of the lips and the extremities, followed by a peculiar, fixed, facetious facial expression; change in personality; diplopia; mental confusion; and disorientation associated with jerking movements of all extremities and jaw muscles, and then generalized convulsions.

Helfer<sup>3</sup> reported a case in which the manifestations of hypoglycemia were dizzy spells, blindness, headaches, fatigue, and periods of amnesia.

Rayner and his associates<sup>4</sup> reported a case of hypoglycemia in a 46-year old woman. During one spell of unconsciousness the patient was incontinent of urine and about the same time neurologic signs, patellar and ankle clonus and plantar responses, were elicited. A diagnosis of hysterical fits had previously been made.

Conn<sup>2</sup> reported the case of a 16-year old girl who had periodic attacks of unconsciousness occurring once or twice a month, each attack usually beginning with visual disturbances, followed by involuntary shaking of the extremities and irrational chattering. Following the attacks, a mild disorientation persisted. A diagnosis of epilepsy had been made, but studies revealed this to be a case of functional hyperinsulinism resulting in hypoglycemia.

Another of Conn's patients,<sup>2</sup> a 47-year old man, suffered from attacks characterized by excessive perspiration, vomiting, incontinence, drowsiness, disorientation, followed by unconsciousness. The attacks ended gradually, but the patient remained disoriented for many hours and there was complete amnesia for the attacks. A diagnosis of intracranial tumor had been made. The hypoglycemia in this patient was discovered to be hepatogenic.

Ziegler<sup>5</sup> reported the case of a middle-aged man who was troubled by somnambulism, states of confusion, and amnesia. After hospitalization for

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psychiatric observation he was at times maniacal. It was discovered that his symptoms occurred concomitantly with a dangerously low blood sugar level.

McClenahan and Norris<sup>6</sup> reported the case of a truck driver, previously very careful and never arrested, who began to have attacks of amnesia during which he committed numerous traffic violations. These attacks were found to be due to hypoglycemia.

The neuropsychiatric manifestations of insulin reactions in diabetic patients have been the subject of numerous reports in the literature. Disorientation, emotional instability, difficulty in concentration, mental confusion, faintness, diplopia, and cardiac palpitation have occurred separately or in combination. Headaches are frequently encountered, especially with the slowly acting protamine zinc insulin. Manifestations are at times mistaken for those due to alcoholic intoxication, especially combinations including dizziness, impairment in gait, and slurred speech. As an example of the emotional and personality changes of this type of hypoglycemia the case reported by Leyton is cited. A diabetic "invited some friends to a meal and began by pressing them to help themselves more liberally to pepper; then, most excitedly in a loud voice, he hurled insulting epithets at his wife who, recognizing the condition, besought him to take some sugar. He replied that of course she wanted him to take sugar, a thing the doctor had forbidden him, so that she might get rid of him, and marry someone else. This patient was finally forced to take sugar; the symptoms passed within half an hour and he had no recollection of what occurred."<sup>7</sup>

So bizarre a pattern of signs and symptoms may occur in the presence of hypoglycemia, and so frequently emotional and psychic disturbances, that a variety of erroneous diagnoses have been made. Among these are epilepsy, narcolepsy, intracranial tumor, diffuse disease of the brain and spinal cord, psychosis, psychoneurosis, neurasthenia, and gastrointestinal disorders.

This close relationship between the signs and symptoms of hypoglycemia and the nervous system represents the effects of low blood sugar concentration on the central and sympathetic nervous system. The extreme sensitivity of the brain to hypoglycemia is due to the fact that it is the only organ which obtains its energy from the combustion of carbohydrate alone. Other organs of the body support their metabolism by oxidation of both carbohydrate and fat. When the blood supply of carbohydrate is decreased, the various non-nervous tissues of the body maintain their activities normally at the expense of energy derived from the oxidation of fat. The brain cannot do this, for it has no foodstuff as an alternate for carbohydrate; its metabolism slows down and the cerebral function suffers.<sup>8</sup>

Furthermore, the newest portion of the brain, the cerebral cortex, has the highest rate of metabolism of all nervous tissue and is therefore the first to suffer from decrease in blood sugar concentration.<sup>8</sup>

Therefore, the possibility of hypoglycemia, whatever the cause be, must be borne in mind, especially in neuropsychiatric work.

## PRESENT DATA

We recently had occasion to study two patients on the neuropsychiatric service of this hospital in whom this possibility had to be entertained in the differential diagnosis.

## CASE REPORTS

Our first patient was a 21-year old private, sent to the hospital with the diagnosis of post-traumatic psychosis. Following an auto accident, seven years before, he had experienced spells of nervousness, jumpiness, and tenseness at loud noises; he had had infrequent attacks of headache and blurred vision following which he had become unconscious. In his voyage to this theatre he had fallen during such an attack and had struck his head.

Early in his hospital stay he was observed in several mild attacks; they were preceded by a sensation of "light headedness." He complained of headache and became confused; there were a few light convulsive muscle spasms in the arms and legs; and his speech was incoherent and barely discernible. In one attack he wandered to the wrong ward at bedtime and prepared to retire; it was necessary to help him back to his ward because of difficulty in his gait. In another attack he fell to the floor unconscious, and had a mild convulsive seizure. There was a total amnesia for the attack.

After preparation on a diet yielding at least 355 grams of available glucose daily,<sup>9</sup> a glucose tolerance test revealed these values:

|               |                     |
|---------------|---------------------|
| Fasting.....  | 80 mg. per 100 c.c. |
| 1st hour..... | 100 mg.             |
| 2nd hour..... | 95 mg.              |
| 3rd hour..... | 71 mg.              |
| 4th hour..... | 91 mg.              |
| 5th hour..... | 74 mg.              |

A glucose tolerance test was then planned, to be performed after a provocative, low-carbohydrate diet,<sup>2, 9</sup> but just prior to the institution of the diet the patient had a moderately severe attack, occurring six hours after his last meal. A blood sugar determination during this attack revealed a concentration of 91 mg. per cent. This ruled out hypoglycemia as the cause of his symptoms.

Our second patient was a 26-year old Private 1st class, sent to the hospital with a diagnosis of chronic syncope. For the past three years, while in the service, he had experienced attacks during which he had "black-out" spells, namely, partial to total loss of vision associated with loss of consciousness, and followed by intense headaches, and then dizziness. They varied in duration from a few minutes to two hours. There was no amnesia.

He had experienced similar attacks for four years prior to his entering the service and during one of these attacks in civilian life he had fallen into a hot aluminum solution and had incurred burns about the face. Some of the attacks occurred prior to meal times, when, he remembered, he had been hungry; some had occurred during the night; however, some attacks had occurred not long after a meal.

Because of the amblyopia, he was studied first on the ophthalmologic service, but no organic ophthalmologic disease was present to account for his symptoms. The patient was accepted on the neuropsychiatric service for further observation.

In the study of his carbohydrate metabolism, he was given first a diet of 310 grams of carbohydrate, 70 grams of protein, and 100 grams of fat, which yielded 355 grams of available glucose daily. Following this preparatory diet,<sup>9</sup> a glucose tolerance test revealed these values:



|               |                     |
|---------------|---------------------|
| Fasting.....  | 63 mg. per 100 c.c. |
| 1st hour..... | 80 mg.              |
| 2nd hour..... | 71 mg.              |
| 3rd hour..... | 71 mg.              |
| 4th hour..... | 67 mg.              |
| 5th hour..... | 74 mg.              |

The fasting level is relatively low, but not below the critical level of 50 mg. per cent.<sup>2</sup> Though the curve is "flat," there are no hypoglycemic levels, and the curve is interpreted as not abnormal.

The provocative, low carbohydrate diet<sup>2, 9</sup> was then given him. It comprised 25 grams of carbohydrate, 35 grams of protein, and 70 grams of fat, yielding 50 grams of available glucose daily. After three days on this diet, a glucose tolerance test revealed these values:

|               |                     |
|---------------|---------------------|
| Fasting.....  | 62 mg. per 100 c.c. |
| 1 hour.....   | 154 mg.             |
| 2 hours.....  | 80 mg.              |
| 3 hours.....  | 43 mg.              |
| 3½ hours..... | 60 mg.              |
| 4 hours.....  | 65 mg.              |
| 4½ hours..... | 111 mg.             |
| 5 hours.....  | 115 mg.             |

Again the fasting level is low, but not below the critical level. The drop to the hypoglycemic level of 43 mg. per 100 c.c. was accompanied by these clinical findings: The patient began to tremble, was flushed, and began to perspire profusely. He was nervous and "shaky"; had a dull temporal headache, was dizzy, and had diplopia. He stated that he felt just like he had felt in the early parts of his previous attacks—that he was going to faint—but he did not lose consciousness.

This established the diagnosis of hypoglycemia as the cause of his symptoms, and with the data at hand, the basic diagnosis, functional hyperinsulinism, was made.

## DISCUSSION

The question arises as to why this patient, who had previously experienced these attacks regularly and frequently, did not have a single spontaneous attack while in the hospital. The explanation seems to be that garrison duty, just as moderate work of any kind, imposed moderate energy demands upon the body metabolism. Furthermore, while in combat, ingestion of food was at times irregular in both time and content. On one occasion in combat, the patient was "pinned down" without food for 36 hours. A further important factor is the release of epinephrine during the entire combat period, reflecting the emotional state, and resulting in fluctuations of blood sugar concentrations.

In contrast to this, while in the hospital, he had access to regular, well-balanced feedings, feedings relatively high in protein content and lower in carbohydrate content than field rations. Furthermore, while on the ward, and later on light duty at the hospital, his activities required but mild exertion. Thus, he was physiologically protected.

Another question arises as to why the first glucose tolerance test did not disclose this abnormality, whereas the second one did. Again, the data at hand provide an adequate explanation. The first test was performed after a full, adequate diet and hence the patient's tolerance was good; that is, he

was able to cope so satisfactorily with a large dose of glucose that no high concentration of glucose occurred post-prandially to stimulate insulogenesis. The effect of the starvation diet, however, was to lower his tolerance. He could not tolerate this high dosage without the building up of a high concentration of sugar in the blood. The insulogenic stimulus level was reached and passed, an excess amount of insulin poured into the blood, and hypoglycemia resulted.

The basic cause of functional hyperinsulinism appears to be an increased responsiveness of the pancreas to the normal insulogenic stimulus, resulting in an outpouring of insulin in amounts greater than required.<sup>2</sup> The treatment then would seem to be along lines aimed at eliminating peaks of post-prandial hyperglycemia. A diet low in carbohydrate and high in protein would seem therefore to be indicated, for the derivation of glucose at a slow, even rate from protein, which in itself is slowly absorbed, would tend to prevent the post-prandial rise in blood sugar.<sup>10, 11</sup> The lower blood sugar levels after meals would really act as insulogenic depressors. This was found to be so<sup>10, 11</sup> and such a diet seems to be the best treatment.

### CONCLUSION

1. Manifestations of hypoglycemia have been presented.
2. Several patients, reported in the literature, have been described.
3. The extreme sensitivity of the central nervous system to hypoglycemia has been pointed out.
4. A patient under neuropsychiatric observation at this hospital, and in whom hypoglycemia was a possibility, has been presented. Adequate study ruled out this diagnosis.
5. Another patient studied on the neuropsychiatric service of this hospital has been reported and along with this a description of the method of study. The suspicion of hypoglycemia as the cause of his symptoms was verified, and the basic diagnosis of functional hyperinsulinism was made.
6. The cause of this disturbance and its dietary treatment have been discussed.
7. And finally, emphasis has been put on the importance of keeping hypoglycemia in mind as a cause of bizarre groups of symptoms, symptoms of so-called "nervous" origin.

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# BLOOD PLASMA PROTEINS IN PATIENTS WITH HEART FAILURE\*

By GEORGE R. HERRMANN, M.D., Ph.D., F.A.C.P., *Galveston, Texas*

THE recognition of oligoproteinemia and more specifically hypoalbuminemia and successes in correction of the significant abnormalities are now commonplace in modern scientific medical practice. Blood plasma protein determination has become practically a routine procedure in diagnostic studies in medical clinics and in our cardiovascular service.

Whipple<sup>1</sup> has summarized the data on the production and utilization, interrelations and modern concepts of plasma protein metabolism. He pointed out that food proteins, after digestion, yielded amino acids which were absorbed from the intestinal tract and carried to the liver. The liver is strategically situated and of sufficient size to perform most of the work of protein synthesis. Some other body cells may perform the function, but most of the plasma proteins seem to emerge from the liver cells and can be utilized in the body for all or most of the protein requirements.

Liver cells can store protein or release fabricated protein. The reserve of plasma protein forming material is considerable, one to five times the circulating mass. The reserve can be reduced by fasting, low protein diet, poor absorption or inadequate rebuilding of plasma proteins or depletion by blood loss. Body protein stores, plasma protein levels, protein production and protein wear and tear are in a state of dynamic equilibrium.

Blood plasma proteins seemingly can pass readily, according to Whipple,<sup>1</sup> from plasma into cells and the reverse without the loss of nitrogen. The proteins need not be reduced to amino acid constituents as formerly thought, but seem to penetrate by preliminary absorption and ultimate penetration into cells. The whole protein on the cell membrane is considered to be modified by contained ferments. The membrane is thought to be composed of bimolecular layer of lipid molecules between two layers of protein molecules.

Protein on its way out or into the cell is designated as transition protein, which by cleavage and reassemblage will be on its way either to become cell protein or to become plasma protein. Once a cell protein can not be removed it is called indispensable. Any parenchymal cell or tissue can act to store, to utilize, to release and perhaps to fabricate plasma proteins in a small way.

## OUR STUDIES

During the past 15 years<sup>2a, b, c, d</sup> we have determined in the clinical biochemical laboratory, rather routinely, the serum proteins and the albumin

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fraction in patients with various diseases, but particularly in those with congestive heart failure with and without hepatic engorgement and edema.

It has been demonstrated that hypoalbuminemia may be the result of one or more of the generally accepted causes. A dilution factor incident to the variable grade but usual hydremic plethora of heart failure must be recognized. The loss of excessive amounts of serum albumin through a defective glomerular filter is admittedly of some significance in patients with congested kidneys, but is more significant in patients with the nephrotic syndrome. There may be lack of building up of the serum albumin or anabolism may be adversely affected as are other hepatic functions in an engorged liver of heart failure. Chavez, Sepulveda and Ortega<sup>3</sup> have demonstrated disturbed liver function tests in patients with congestion of the liver in right ventricular failure. Serum albumin is most markedly

ARTERIOLEAR, CAPILLARY AND VENULE BLOOD PRESSURES  
V.S. COLLOID OSMOTIC PRESSURES IN EDEMA FORMATION

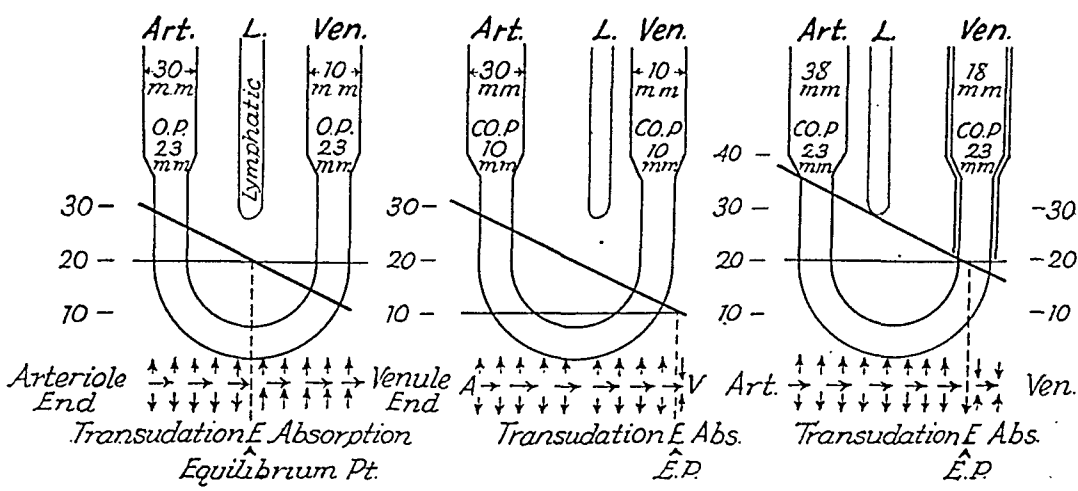


FIG. 1.

decreased when there is disease of the liver, as cirrhosis which may at times be the result of chronic congestion.

Apparently the factor of the gradual development of liver insufficiency that comes with cardiac cirrhosis is important. Katzin, Waller and Blumgart<sup>4</sup> and Garvin<sup>5</sup> have shown that increased fibrous tissue occurs in about one-third of all cases of chronic congestive failure three times as frequently as in all patients that died without congestive heart failure. It, therefore, seems worthwhile to consider liver changes as significant.

A diseased or congested gastrointestinal canal may interfere somewhat with absorption or with the breaking down of complex protein into amino acids for rebuilding. Anorexia may contribute further to decreased intake of food protein of good biological character. Starvation is not as important

a cause of hypoalbuminemia in this country as it is in the enemy occupied and recently liberated countries.

The increased permeability of the capillary walls as the result of toxins or anoxia in patients with severe heart disease might account for edema in some instances. This factor, however, has been practically ruled out by subsequent studies. The rôle of hypoalbuminemia as schematically represented in figure 1, has been minimized in the mechanism of edema of myocardial insufficiency. The postural rise in the venous pressure incident to circulatory failure, intensified by increased hydrostatic pressure in the veins of the dependent part, may be chiefly responsible for edema. The retention of sodium in the tissues as the result of disturbed electrolyte distribution must be considered, though it rarely is the sole factor in edema formation. All three factors combined in various grades usually may be incriminated in the production of edema in patients with congestive heart failure.

It was realized from the beginning that there were several factors concerned in the disturbed water-balance in congestive circulatory failure with edema formation. Venous pressure and the electrolyte levels, as well as the blood serum proteins, were studied in the presence of, during and after the dissipation of the edema.

#### STANDARD METHODS USED

The total blood proteins have been determined and the albumin fraction and the globulin fraction have been separated by the salting out method and determined by the colorimetric reaction of Folin or by the micro-Kjeldahl and Nesslerization for total nitrogen and subtraction of the non-protein nitrogen. The blood specific gravity, as determined by the falling drop is more simple and probably accurate enough, but is applicable only for total plasma protein levels. We only recently have begun to use it. The absolute total blood volumes and shifts were followed in many cases by application as the new accurate method of Gregerson, Gibson and Stead as modified by Gibson and Evelyn using the Evans Blue Dye No. 1824 and a photoelectric colorimeter. These methods were used in the analysis of blood serum obtained from practically every patient on admission, the morning after diuresis was completed, at weekly intervals, and upon discharge from the hospital.

#### PRESENT DATA

The mass of clinical and laboratory data that has accumulated in our records from the beginning is made up of thousands of determinations and could not possibly be entirely analyzed at this time. Case records of 100 completely studied patients in congestive heart failure were drawn from the files at random. Many of these patients had had numerous studies during various admissions. The great majority of them suffered from hypertensive heart disease, coronary arteriosclerosis and chronic myocardial

insufficiency with congestion of the viscera and edema. There were some cases of syphilitic heart disease and an occasional case of rheumatic heart disease. Most of the patients having frank cirrhosis of the liver were removed from the 100 and substitutions were made.

For comparison the data on 100 patients with edema and congestive heart failure and 46 in whom the edema had cleared are presented in table 1. The normal values that we have obtained previously and those in the literature give mean values of 4.80 gm. per cent (range 4.20 to 5.65) for albumin; 1.90 gm. per cent (range 1.32 to 2.91) for globulin; and 6.70 gm. per cent (range 5.60 to 7.65) for total proteins.

The mean levels for albumin in cardiac patients with edema was 3.54 gm. per cent with a standard deviation of  $\pm .793$ ; for globulin 2.58 gm. per cent with a standard deviation of  $\pm .720$  and for total proteins 6.06 gm. per cent with a standard deviation of  $\pm .874$ . These are slightly but significantly lower than corresponding values obtained later in the same patients.

TABLE I  
Blood Serum Proteins in Congestive Heart Failure with and without Edema

|                        | Mean Alb. | Stand. Dev.        | Mean Glob. | Stand. Dev.        | Mean Total | Stand. Dev.        | Mean V.P. cm. | Stand. Dev.       |
|------------------------|-----------|--------------------|------------|--------------------|------------|--------------------|---------------|-------------------|
| 100 Pts. Edema Present | 3.54      | .793+-             | 2.58       | .720+-             | 6.06       | Grams%<br>.874+-   | 17.9<br>(54)  | .477+-            |
| Free of Edema (46)     | 3.62      | .667+-             | 2.65       | .797+-             | 6.12       | Grams%<br>.984+-   | 14.03<br>(9)  | .485+-            |
| Normal Range           | 4.80      | 4.20<br>to<br>5.65 | 1.90       | 1.32<br>to<br>2.91 | 6.70       | 5.60<br>to<br>7.65 | 9.0           | 8.0<br>to<br>10.0 |

In 46 patients that became edema-free the mean levels for the albumin were 3.62 gm. per cent with a standard deviation of  $\pm .667$ ; for globulin 2.65 gm. per cent with standard deviation of  $\pm .797$ ; for total proteins 6.12 gm. per cent and standard deviation of  $\pm .984$ . The differences are relatively small suggesting that full recovery lags behind diuresis.

The venous pressures, on the other hand, in 54 cases during the period of edema showed a mean of 17.9 cm. of water and a standard deviation of  $\pm .477$ . In the edema-free cases, only nine of which were recorded, the venous pressure was lower with a mean of 14.03 cm. of water and a standard deviation of  $\pm .485$ , which is a significant difference. The shifts in the electrolytes, particularly in the sodium ion, were not studied in enough cases thus far to warrant giving this element the position of significance that it probably deserves.

For comparison similar data on 20 cases of apparently irreversible cirrhosis of the liver showed lower values; mean albumin 2.58 gm. per cent with standard deviation of  $\pm .536$ ; mean globulin 3.07 gm. per cent with

standard deviation of  $\pm .937$ ; mean total proteins 5.69 gm. per cent with standard deviation  $\pm 1.034$  and the mean venous pressure was 13.06 cm. with standard deviation of  $\pm 3.11$ .

In eight patients with no ascites the mean albumin level was 3.48 gm. per cent with standard deviation of  $\pm .501$ ; mean globulin 2.77 gm. per cent with standard deviation of  $\pm .829$ ; mean total proteins 6.37 gm. per cent with standard deviation  $\pm .706$  and mean venous pressure was 11.08 cm. with standard deviation of  $\pm .092$ .

### DISCUSSION

Our early studies <sup>2a</sup> (1930), <sup>2b</sup> (1931), <sup>2c</sup> (1932) and those of others <sup>6, 7, 8</sup> suggested that lowered oncotic pressure incident to hypoalbuminemia was at least a recognizable factor in edema formation of congestive heart failure. Stewart <sup>9</sup> disagreed. However, our conceptions are supported by data furnished by further studies which have been subsequently carried out and have not been included in this paper.

TABLE II  
Blood Serum Proteins in Cirrhosis of the Liver with and without Ascites

|                              | Mean Alb. | Stand. Dev. | Mean Glob. | Stand. Dev. | Mean Total | Stand. Dev.       | Mean V.P. cm. | Stand. Dev. |
|------------------------------|-----------|-------------|------------|-------------|------------|-------------------|---------------|-------------|
| 20 Pts. Ascites present (20) | 2.58      | .536+—      | 3.07       | .937+—      | 5.69       | Grams%<br>1.034+— | 13.06<br>(6)  | 3.11+—      |
| Free of Ascites (8)          | 3.48      |             | 2.77       |             | 6.37       | Grams%<br>.706+—  | 11.08<br>(2)  |             |
|                              | .501+—    |             |            | .829+—      |            |                   |               | .92+—       |

The blood serum proteins had been determined in our cardiovascular service in hundreds of other patients with congestive heart failure with edema and after the edema had been rapidly removed by powerful diuretics. Only slight, if any primary effective or persistent plasma protein changes have been recorded during active diuresis in our laboratory.<sup>10</sup> In acute studies with Calvin and Decherd<sup>10</sup> during which great shifts in blood volume were induced in congested cardiacs by diuretics, the albumin fraction was found to shift temporarily as required for maintenance of colloid osmotic pressure. There was evidence that there was an outflow of proteins from and a backflow into the tissues during and after acute diuresis.

The absolute total blood plasma volume has been recognized as increased in congestive failure from 20 per cent to as much as 50 per cent with a slightly greater proportion in erythrocytes than in plasma. However, the decrease on treatment was from 2 per cent to 40 per cent averaging 17.5 per cent with wide fluctuations in many cases.<sup>11</sup>

The delay in the rise in blood plasma proteins after the edema was dissipated and clinical improvement was evident and the reversal of the A/G



ratio and its return to normal support the contention that abnormalities in blood proteins are associated with functional changes in the liver incident to the passive congestion. Apparently the elaboration of albumin follows the slower reestablishment of the more normal anabolic capacity of the liver cells. The factor of the gradual development of liver insufficiency and hypoalbuminemia that comes with chronic passive congestion and its resulting cardiac cirrhosis has been neglected.

The lowering of the blood serum proteins, particularly the albumin fraction, as a significant effect of hepatic cirrhosis is emphasized in similar data from patients with apparently irreversible cirrhosis of the liver with and without ascites (see table). The patients were generally middle-aged and elderly, about two caucasians to one negro, and two males to one female. In these cases steps had been taken with some success to increase the generally low or depleted blood serum protein mass that had developed as a result of the disturbed metabolic processes in the liver. High protein diets supplemented with yeast, casein hydrolysates, amino acid mixtures or choline and methionine have produced spectacular results in some patients with enlarged fatty livers and hypoalbuminemia, in our experience<sup>12</sup> as well as in the hands of others.

#### SUMMARY

The rôle of low blood plasma proteins, particularly low serum albumin, in relation to edema formation in patients with congestive heart failure has been investigated.

The results of our previous studies have been substantiated and the blood plasma protein studies on 100 edematous patients with congestive heart failure analyzed. These showed slightly, but definitely subnormal albumin levels with slight compensatory increases in globulin values.

After the dissipation of the edema the blood proteins did not immediately rise to normal levels but there were gradual accretions. It is suggested that the lag may well be due to and evidence of liver dysfunction. Time is required after diuresis and reestablishment of circulatory equilibrium for liver function to be restored and normal protein anabolism to become effective.

The lowest blood protein levels were noted in patients who had had congestive failure for many months and especially in those who developed evidences of cirrhosis of the liver. Irreversible cirrhosis is shown to result in still lower blood serum albumin values.

Feedings of high protein, acid or neutral ash as well as sodium free, diets are indicated in most patients with congestive heart failure and edema. Proteins of good biological character may be supplemented with protein hydrolysates, amino acids, yeast or choline.

I am indebted to my daughter, Gretchen S. Herrmann, A.B., for stimulating me to work up the material on the first 50 clinical cases that she had analyzed and to Mr. Howard Monk for helping me to complete the study of the other 50 cases and 20 cases of cirrhosis of the liver.

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# CASE REPORTS

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## MASSIVE DOSES OF PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS\*

By NOYES L. AVERY, JR., Major, M. C., ORLANDO B. MAYER, Col., M. C.,  
F.A.C.P., and ROBERT C. NELSON, Captain, Sn. C., A.U.S.

RECENTLY an impressively high percentage of apparent cures in cases of subacute bacterial endocarditis has been reported by treatment with penicillin. In most of these cases the infecting organism has been a *Streptococcus viridans*. Some strains of this organism, unfortunately have been resistant to penicillin. We wish to report such a case which, although apparently incurable with rather large doses of penicillin, did respond favorably when massive doses of penicillin were employed in the presence of a renal blockage with diodrast and sodium p-aminohippurate. It should be noted that in this case, during the 17 month period in which various doses of penicillin were given, the organism seemed to become increasingly resistant to penicillin.

The method used for determining penicillin sensitivity was as follows: Dilutions of penicillin were set up in (a) thioglycolate broth (Difco) and (b) tryptose-phosphate broth (Difco). A standard inoculum of the streptococcus involved was added to each dilution. End points were determined by subculturing on tryptose agar after 72 hours. It was found that the 72 hour end point was in agreement with subsequent end points determined as long as 10 days after inoculation. The end point used was the smallest amount of penicillin producing negative subcultures after 72 hours incubation of the dilution-culture. The amount required to inhibit growth of the organism was found to be considerably below the lethal requirement. Medium used for blood cultures was Difco tryptose-phosphate broth. Subcultures were made with poured plates of tryptose agar.

The following is a summary of the methods used in determining the concentration of penicillin in blood serum:

1. A solution of penicillin was standardized by the inhibition zone method using the Oxford strain *Staphylococcus aureus*. This solution was used as control for all penicillin serum-level determinations.

2. The determinations were done by two methods: (a) Using Type "O" erythrocytes and a hemolytic streptococcus (Oxford) plus test serum dilutions. The end point for this method was the greatest serum dilution showing no hemolysis of the erythrocytes. (b) Using the Oxford strain *Staphylococcus aureus* in dilutions of the test serum. The highest dilution of serum showing no turbidity was taken as the end point. In both methods as controls known amounts of penicillin were substituted for the serum dilutions and the amount of penicillin in the serum was computed by comparison of the end point dilution

\* Received for publication December 13, 1945.

factors of the control and the test series. In all cases when determinations were made on a serum specimen the results were in agreement.

### CASE REPORT

A First Lieutenant bomber pilot, aged 28, first came under our observation on September 2, 1944. The family history was interesting in that his father had died of subacute bacterial endocarditis about five years previously. When the patient was four years of age his family had been informed that he had a systolic heart murmur which was probably not considered clinically significant. There was no history of either rheumatic fever or definite congenital heart disease. The Officer stated that he believes a heart murmur was detected when he entered the service December 7, 1941, but this murmur was again not considered clinically significant. Subsequent examinations during the training period evidently revealed no disqualifying defects and he was commissioned as a pilot June 23, 1942.

On about April 1, 1943, while on duty in North Africa, he first noted the insidious onset of chilliness and fever. During the following month no cause for this fever could be found, but on clinical grounds he was given antimalarial therapy without effect.

On about May 11, 1943 the fever became more marked, accompanied by malaise, generalized aching, and migratory joint pains without any objective evidence of joint disease. The physical examination at that time was normal except for a loud, widely transmitted, harsh systolic murmur at the apex of the heart. He was evacuated to the United States, arriving on August 30, 1943. While in transit he had his first cerebral episode manifested by unconsciousness and a temporary monoplegia of the left arm. On September 22, 1943 a blood culture first became positive for a slow-growing *Streptococcus viridans*. Following a short course of sulfadiazine therapy, he was transferred to another Army hospital where penicillin was available. A note appeared in the clinical record that "fortunately this organism is very sensitive to penicillin", but the evidence for this statement was not further elaborated. During the course of this hospitalization, from November 11, 1943 to August 28, 1944, multiple courses of penicillin therapy were given the patient. His temperature curve usually ranged from 99° to 101–102° F. daily when not under therapy. The various schedules included (a) 120,000 U penicillin IM per day; (b) 200,000 U penicillin IM per day; (c) 200,000 U penicillin IV per day; (d) 100,000 U penicillin plus 100 to 200 mg. sodium heparin IV per day. These schedules all resulted in temporary benefit, but gradually the temperature curve would return to its usual daily swing to 101–102° F. and the blood cultures would remain positive even though under therapy. From November 11, 1943 to August 28, 1944 (when treatment was temporarily stopped) the officer had received a total of 32,000,000 U penicillin. His general clinical condition remained surprisingly good and his spirits optimistic.

At the time of admission to our hospital on September 2, 1944 he presented a picture of a pallid, fairly well nourished, chronically ill individual. The heart was considered slightly enlarged clinically and perhaps by roentgen-ray, and there was a loud, harsh, apical, systolic murmur associated with an easily palpable thrill. Initially we noted rather definite evidence of congestive failure with a gallop rhythm, basilar pulmonary râles, an increase in the subcutaneous fluid, and a persistent hacking cough. These signs disappeared with usual type of therapy and during our first course of penicillin therapy. The blood counts were consistently within normal limits except that the red blood cell count varied between 4.0 and 4.5 million per cu. mm. The urine often showed few to many red blood cells and small amounts of albumin, although it was more usually normal. Electrocardiograms and blood urea nitrogen determinations were always normal. There were many episodes of showers



and there were still occasional episodes of petechiae. During this 17 day period 51,000,000 U penicillin were given. Since the blood level did not exceed 1.0 unit per c.c., it was believed advisable to employ diodrast as a means of producing a renal blockade.<sup>2</sup>

Accordingly, diodrast was given as follows (see table): Penicillin 1,500,000 U per day IV with 40 mg. of sodium heparin by continuous intravenous drip was given for three days to establish a control blood level, namely 0.4 Oxford unit per c.c. At noon on April 5, 1945 diodrast was added intravenously in the amount of 7.5 c.c. of a 35 per cent solution hourly for a period of 70 hours. The penicillin blood level increased rapidly to 2.4 and 3.2 units per c.c. at the end of 24 and 70 hours, respectively. By 24 hours after the diodrast was terminated, the penicillin level in the blood was still 1.0 unit per c.c. The diodrast itself was believed responsible for the temperature elevation to 101° F. on April 6, 1945. No other ill effects were noted.

Through the courtesy of Sharp and Dohme, a supply of sodium p-aminohippurate was obtained, the use of which to produce a renal blockade had been suggested by Beyer and coworkers.<sup>3, 4</sup> Again a three-day control period was run with a continuous intravenous drip of 1,500,000 U penicillin and 40 mg. of heparin, obtaining a constant blood level of 0.5 Oxford unit of penicillin per c.c. A priming dose of 20 grams of sodium p-aminohippurate was given intravenously on the third day and thereafter 120 grams per day were added to the intravenous solution. The blood penicillin concentration rose to 2.0 U per c.c., four times the control level. Again a mild febrile response occurred with the use of this drug, but it soon subsided. The schedule was terminated on April 21 when our supply was exhausted on the ninth day of its use. After this date no further therapy of any kind was given. The temperature curve following April 20 remained quite normal, confirming our clinical impression that the above-mentioned febrile reactions were presumably due to diodrast or p-aminohippurate.

The blood culture obtained on March 5, 1945 was the last one to become positive for the streptococcus. Blood cultures taken on April 23 and 24 and May 4 and 21 were reported negative after 23, 22, 15 and 14 days respectively. From March 13 to April 21 a total of 80,250,000 U penicillin were given. Prior to September 2, 1944, 32,000,000 U had been administered and 39,880,000 U were given by us prior to March 1945 without more than temporary clinical improvement. This made a grand total of 152,130,000 U penicillin throughout.

#### COMMENT

It is too early to evaluate this case in terms of a cure. A recurrence with the same or another organism may occur in the future. However, it is noted that after April 21, 1945 the patient was continuously afebrile for the first time in two years, with negative blood cultures since March 5, 1945. He is now ambulatory and shows no signs of activity.

Our plan for penicillin therapy in future cases will be first to determine the specific organism's penicillin sensitivity and then by appropriate means, with or without renal blockage, to obtain penicillin blood levels two or three times those necessary to kill the organism in vitro. It would appear in retrospect that had the plan been attempted earlier, the large amounts of penicillin finally employed would not have been necessary. We believe that these conclusions are valid and offer a rational and concrete approach to penicillin therapy in subacute bacterial endocarditis.

## SUMMARY

The plan for penicillin therapy in cases of subacute bacterial endocarditis is presented. Over a period of approximately 17 months a total dosage of 152,-130,000 units of penicillin was administered, but apparent cure was not effected until blood levels exceeded by several times the in vitro penicillin sensitivity of the organism. A method is suggested to obtain high serum penicillin blood levels.

## ADDENDUM

Subsequent blood cultures as of October 4, 1945 were negative. Following increased physical activity the heart became noticeably enlarged, but no recurrence of the endocarditis has been observed.

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## A CASE OF LYMPHOGRANULOMA VENEREUM ASSOCIATED WITH ATYPICAL PNEUMONIA \*

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LYMPHOGRANULOMA venereum is no longer thought of as a local infection of the genitalia, regional lymphatics, rectum, and sigmoid, but as Harrop<sup>1</sup> has described, a systemic infection capable of producing headache, septic fever, chills, sweats, and articular rheumatism, and capable of involving lymphatics other than those of the inguinal and pelvic regions. The patient reacts to this infection with an elevation of serum globulin, thought by Schamberg<sup>2</sup> to be an evidence of humoral antibody response. The skin becomes hypersensitive to the intradermal injection of suspensions of the inactivated virus, the Frei test.

Rake and his coworkers<sup>3</sup> have improved the Frei antigen test for this disease, and in addition have introduced a complement fixation test, as well as a specific antitoxic reaction.<sup>4</sup> The same workers<sup>5</sup> have described similarities and discussed relationships among the viruses of lymphogranuloma venereum, psittacosis, atypical pneumonia and meningopneumonitis.

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When mice are inoculated intracerebrally with the virus of lymphogranuloma venereum, meningitis results. That this experimental finding applies to man was recently shown by Sabin and Aring,<sup>6</sup> who conclusively demonstrated the occurrence of meningoencephalitis in man due to the virus of lymphogranuloma venereum.

When the virus of lymphogranuloma venereum is inoculated intranasally into mice, pneumonia results. The pathological picture in the lungs is quite like that seen in the so-called "virus" or atypical pneumonia of man.<sup>7</sup> The same group of viruses noted above is believed to cause atypical or "virus" pneumonia in human beings.<sup>8</sup>

From the foregoing one might expect to encounter pneumonitis in some cases of lymphogranuloma venereum. We know of no reference in the literature describing this association in man.

The following case report is presented only because of the concurrent presence of both lymphogranuloma venereum and atypical pneumonia.

#### CASE REPORT

A 29 year old colored sergeant was transferred to Percy Jones General Hospital on February 17, 1943. He had been quite well in the past except for an episode of gonococcal urethritis one year before, which had responded promptly to treatment. Family history revealed that his mother had died of tuberculosis some years before. During the month of December 1942 he began to note a hacking cough which had never disappeared. He had no other complaints until he returned from a furlough on January 3, 1943. On this date he began to feel badly, and two days later entered the station hospital at his camp, because of malaise, cough and chills. On admission, his temperature was 104° F., pulse 88, and respirations 24. Physical examination at this time was negative except for impairment of percussion at the right base and roentgenographic evidence of an elevated right diaphragm, but no pulmonary disease. For the next few days, his condition remained essentially the same, his temperature staying at about 102° F. On January 8 he developed severe pleuritic pain on the right and by the next day a pleuritic rub was in evidence as well as bronchial breathing and râles at the right base. Roentgenogram now showed in addition to the elevated right diaphragm, what was interpreted to be pneumonitis (figure 1). Sulfathiazole was administered between January 9 and January 15, with no apparent effect. His temperature gradually came down to normal by January 14 and the white blood count, which had been 18,700 on January 11 soon dropped to 13,400.

During the next few weeks he felt fairly well and was up and about. His only complaint during this time was aching pain in the right axillary region. The roentgenogram now showed gradual clearing, with an area of plate-like atelectasis (figure 2.) On about February 5 he became aware of a somewhat tender swollen lymph gland in the right axilla, which subsided spontaneously within a week. This was followed by gradual enlargement of the lymph glands in the left inguinal region, first noted on February 12. There was slight elevation of temperature at this time. As it became apparent that he was not recovering promptly, he was transferred to the Percy Jones General Hospital on February 17. On arrival, his temperature was 101° F., and he appeared somewhat prostrated. Moderate bilateral axillary adenopathy was present. An enlarged, moderately tender, almond sized node was felt in the left inguinal region. The remainder of the physical examination was negative except for some limitation of motion of the right thorax and signs suggestive of elevation of the right diaphragm.



The initial laboratory studies, including urinalysis, Kahn reaction, blood culture, agglutination for *B. tularensis* as well as culture of lymph from the left inguinal node, obtained by aspiration, were all negative. Red blood cell count and hemoglobin reading were normal but the white cell count was elevated to 12,500 with a normal differential. Blood sedimentation rate was 84 mm. per hour. His temperature, which averaged 102° F. for the first several days after transfer, gradually subsided to normal by March 6. On March 8 the left inguinal gland which had enlarged to the size of a pecan was removed for biopsy. Following this procedure, low grade fever was present for a few days. The wound drained for a time and then gradually healed.



FIG. 1.

The remainder of his hospital course was uneventful except for an episode of cellulitis adjacent to the wound which developed on March 27. This was treated with sulfadiazine and the cellulitis and accompanying fever disappeared within a few days. The sulfadiazine was continued for a period of four weeks and blood levels of 5 to 7 milligrams per 100 c.c. were obtained. All traces of pleural and pulmonary involvement gradually disappeared, only a few adhesions to the diaphragm remaining. There was no remaining adenopathy of note. Because of administrative reasons he was kept in the hospital until August. After a final proctoscopic examination which showed the rectum and sigmoid to be entirely normal he was discharged to duty.

*Laboratory.* Serum albumin was 4.5 and globulin 4.7 grams per 100 c.c. The Frei test was positive repeatedly. Blood sedimentation rate gradually dropped to

normal. Section of the gland which was removed revealed it to be honeycombed with soft yellowish accumulations of pus. Cultures, smears and guinea pig inoculations, as well as tissue stains for organisms, were performed with negative results. The microscopic sections were suggestive of lymphogranuloma venereum. Serum was sent to the laboratory of Dr. Geoffrey Rake, of the Squibb Institute for Medical Research, for complement fixation tests with the virus of lymphogranuloma venereum and related viruses. The patient's serum fixed complement in high dilution with the specific virus, and in much lower dilutions with the other viruses of this group. Like-

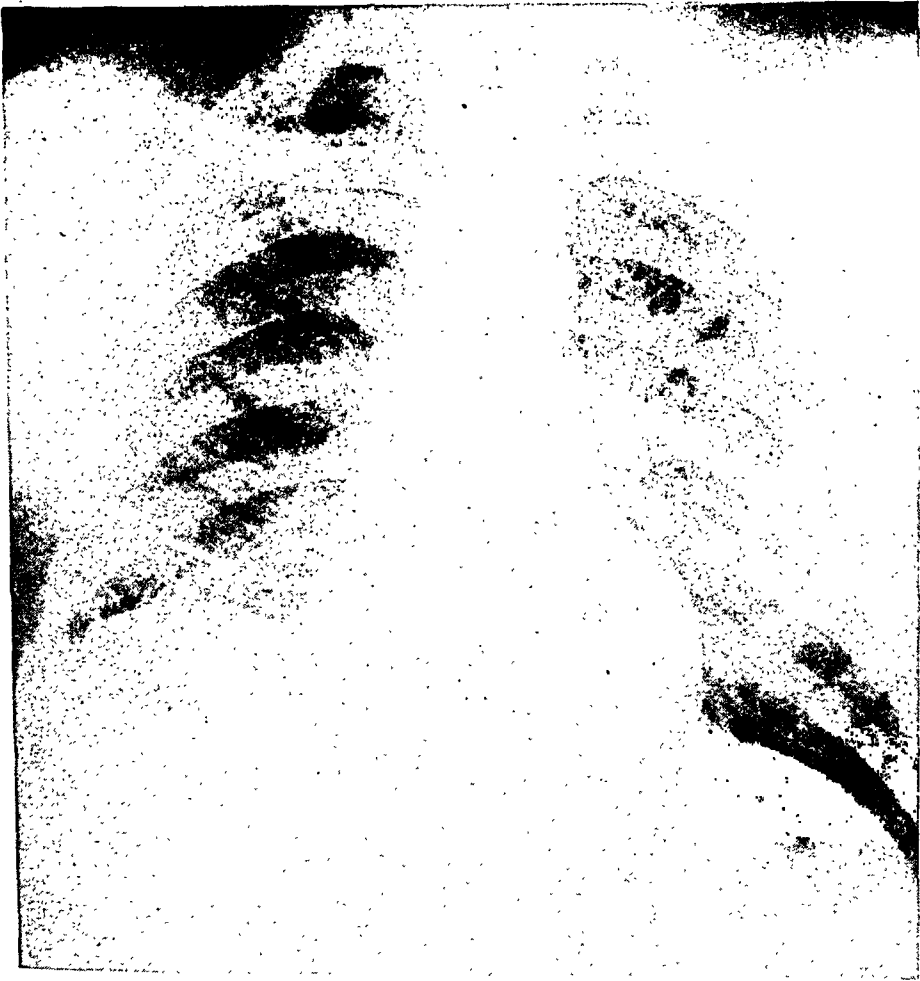


FIG. 2.

wise, the serum exhibited the recently described specific antitoxic reaction. These data convinced us that we were dealing with an acute case of lymphogranuloma venereum and that possibly the one agent was the cause of both pathologic processes.

#### SUMMARY

A case exhibiting pneumonitis and lymphadenopathy accompanied by laboratory evidence of lymphogranuloma venereum is presented. It is suggested that the combination of pathologic processes may have been due to the virus of lymphogranuloma venereum.

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## A CASE OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION IN A NINETEEN YEAR OLD WHITE MALE \*

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CORONARY artery disease exists in young people. Glendy, Levine, and White<sup>1</sup> have reported a series, the youngest patient being 20 years old. Recently French and Dock<sup>2</sup> reported a group of men 20 to 36 years of age all of whom had proved coronary thrombosis with myocardial infarction.

A case of coronary thrombosis in a 19 year old youth is reported.

### CASE REPORT

A patient aged 19 years was admitted to Emergency Hospital January 10, 1945, complaining of severe constant pain radiating across the abdomen just above the umbilicus.

\* Received for publication April 6, 1945.

Eighteen hours prior to admission the patient awoke with abdominal pain described as constant, severe, with no tendency to wax or wane, and not altered by change in position. Prior to retiring the night before, he had felt well following attendance at a party where he ate heartily of cheese, hamburgers, and fruit cake. There was no nausea or vomiting associated with the pain. He had a normal bowel movement in mid-morning. He was not aware of having fever, chills or shortness of breath, but he noted that he had not voided all day.

Late in the afternoon he was visited by a physician who made a diagnosis of acute gastroenteritis and prescribed an antacid which he promptly vomited. An enema was given with good results.

In the past he had had measles, mumps, chickenpox, an appendectomy at the age of five, and scarlet fever at the age of 15. There was no history suggestive of rheumatic fever. Review of systems was completely negative except for strabismus convergens present from birth, for which he was rejected from the armed services.

The family history was entirely non-contributory.

On physical examination he appeared acutely ill, his temperature was 99.4° F., pulse rate 96 per minute, respiratory rate 30 per minute, blood pressure 128 mm. Hg systolic and 84 mm. diastolic. His skin was flushed, warm and moist. There was strabismus convergens of the eyes. The pupils were equal and reacted to light and accommodation. Teeth, tonsils, nose, and throat were normal and there was no rigidity or lymphadenopathy of the neck. The chest was clear to percussion and auscultation. The heart sounds were distant, but quite distinct. Rate was 96 per minute, and rhythm was regular. No murmurs were heard. Tenderness and rigidity of the abdomen were marked; this was more severe in the epigastrium, and there was no localized point of tenderness. There was no referred or rebound tenderness, and no palpable masses. Bilateral costovertebral tenderness was present and percussion over the kidneys produced waves of pain across the abdomen. Peristalsis was active. The extremities were normal and the neurological examination negative.

The hemogram on admission was as follows: Hemoglobin 14 grams per cent or 85 per cent, red blood cells 4,650,000 per cu. mm., white blood cells 26,000 per cu. mm. with a differential count of 95 per cent polymorphonuclear neutrophils, 4 per cent lymphocytes and 1 per cent monocytes. The urinalysis revealed: color amber, slightly cloudy, acid in reaction, specific gravity 1.010, heavy trace of albumin, and negative sugar reaction. Microscopic examination showed numerous epithelial cells, red and white blood cells.

The preliminary diagnosis at this time was: (1) Acute glomerulonephritis; (2) peritonitis; etiology: (a) perforated ulcer; (b) pneumococcal peritonitis.

Treatment was symptomatic and palliative.

The next morning the patient appeared to be worse, the temperature was 101.2° F., pulse rate 120 per minute, respirations were 30 per minute and very labored. The blood pressure was 124 mm. Hg systolic and 80 mm. Hg diastolic. He described the pain as just the same although morphine sulfate gr.  $\frac{1}{4}$  had given him relief. The physical signs were unchanged except it was believed that tubular breathing was heard over the right upper lobe of the lung posteriorly.

Roentgenograms of the chest and abdomen revealed no abnormality. The hemoglobin and red cell count were unchanged, but the white cells had increased to 35,000 with a differential of 92 per cent polymorphonuclear forms, 7 per cent lymphocytes and 1 per cent monocytes. The blood amylase was 142 units (Somogyi, normal 80 to 150). The non-protein nitrogen blood level was 64 mg. per cent. The urinalysis was essentially the same, with a large amount of albumin present and red cells and bacteria in large numbers.

Late in the afternoon the patient complained of pain, burning in character, in both heels, but both feet were warm and of normal color, and the pulsation of the dorsalis pedis arteries was normal. No evidence of thrombosis, either arterial or

venous, could be found. The temperature, pulse, and respirations remained the same.

During the night of January 11, the patient slept at intervals, requiring morphine sulfate gr.  $\frac{1}{4}$  twice to relieve the pain. On January 12, at 7:30 a.m., he stated that the pain was less severe and that he felt better, although it was noted that he was very pale and slightly cyanotic. Oxygen was started. The temperature was now 101.4° F., pulse 108 per minute, and respirations were 28 per minute. By 8 a.m. he was markedly cyanotic and respirations ceased suddenly at 8:15 a.m.

At the postmortem examination the pathological findings were confined to the heart, kidneys and lungs.\*

The pericardial sac contained 3 c.c. of clear, colorless fluid. The heart was enlarged slightly; the surface was smooth and glistening. All the valves were grossly normal. The tip of the left ventricle contained a small intramural thrombus. The descending branch of the left coronary artery contained a well organized thrombus one and one half centimeters in length, within one and one-half centimeters of the origin of the vessel. The heart muscle was mottled, and several yellowish to white areas were noted in the left ventricle. Examination of the interventricular septum revealed a typical myocardial infarction.

Both the lungs hung free in the pleural cavity. The lower right lobe was atelectatic posteriorly, and the remainder was crepitant. The left lower lobe was also atelectatic, and on section moderate edema was present.

Both kidneys were hemorrhagic in appearance, slightly swollen, and contained multiple small early infarcts. On section there was evident extensive acute necrosis due to multiple emboli. The left renal artery was filled with an organized embolus.

Microscopically the heart muscle fibers were of average size, they stained unevenly, and marked fragmentation was noted. There was an advanced degree of acute necrosis of the muscle, and all the vessels were filled with fresh thrombi, and some partially organized thrombi. The muscle tissue was heavily infiltrated with polymorphonuclear cells and large histiocytes containing cellular debris. Hemorrhage was present in some portions.

The thrombosed coronary artery was severely diseased. There was advanced cystic degeneration of the media with a large plaque of atheromatous deposit within the media. The intima was denuded, and part of the adherent thrombus was present. The periarterial tissue was edematous and infiltrated by red blood cells, lymphocytes and plasma cells.

Section through the mural thrombus showed it to be a well organized clot with dense bands of fibrin, and infiltrated with large mononuclear cells, lymphocytes and polymorphonuclear cells.

The lungs were intensely congested. The alveoli were partially atelectatic and contained many "heart failure cells."

The kidney parenchyma was widely destroyed as a result of multiple hemorrhagic infarcts. Many vessels were filled with fresh thrombi, and a few contained portions of organized emboli. One fair sized artery was completely occluded by an organized embolus which had become incorporated with the vessel wall. The infarcted tissue was hemorrhagic and heavily infiltrated by polymorphonuclear cells, and the intervening tissue was completely necrotic. It was also noted that those glomeruli which had not undergone acute infarction or secondary necrosis were badly fibrosed; and there was an unusual degree of sclerosis of the afferent arterioles. Some of the other arterioles were completely occluded and others narrowed. This was a most severe degree of arteriolar sclerosis.

The final diagnosis was: (1) Acute coronary thrombosis with myocardial infarction; (2) severe coronary atheromatosis with medial cystic degeneration; (3) multiple renal infarcts; (4) marked arteriolar sclerosis.

\* Postmortem examination by Dr. Charles Eronstein.

## SUMMARY

A case of coronary thrombosis with coronary artery sclerosis, renal infarction and arteriolar sclerosis, with postmortem findings, in a 19 year old white male is reported.

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PAROXYSMAL VENTRICULAR TACHYCARDIA ASSOCIATED  
WITH SHORT P-R INTERVALS AND PROLONGED  
QRS COMPLEXES \*

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SIDNEY D. LEO, Captain, M.C., A.U.S.

ALTHOUGH earlier writers,<sup>1, 2, 3</sup> had discussed the syndrome of short P-R intervals and widened QRS complexes, proper clinical evaluation of the problem was not accomplished until the paper of Wolff, Parkinson, and White,<sup>4</sup> by whose names the syndrome is frequently known. These earlier papers referred to the relative frequency of associated paroxysmal auricular tachycardia or auricular fibrillation.

Recently interest has been renewed in the syndrome because of its occurrence with paroxysmal ventricular tachycardia. The first report apparently was that of Arana and Cossio in 1938,<sup>5</sup> whose patient had episodes of auricular fibrillation and paroxysmal ventricular tachycardia associated with this syndrome. In 1940 Hunter, Papp, and Parkinson<sup>6</sup> described two patients in whom the syndrome occurred with paroxysmal ventricular tachycardia; one of the patients subsequently developed a supraventricular tachycardia, the other auricular fibrillation. Three additional cases of Wolff-Parkinson-White syndrome and paroxysmal ventricular tachycardia were described by Levine and Beeson<sup>7</sup> in 1941. A more recent report by Palatucci and Knighton<sup>8</sup> describes a similar case. Many of the above writers comment on the difficulty of excluding recent myocardial infarction in some of these patients.

The patient herein described represents another example of paroxysmal ventricular tachycardia associated with short R-R intervals and wide QRS complexes. Certain features of this case would seem to justify the addition of another report to the literature.

## CASE REPORT

A 20 year old flying officer was admitted to the hospital on February 29, 1944 complaining of a "grabbing" pain in the epigastrium and sternum which was aggravated by effort and diminished by rest.

\* Received for publication April 14, 1945.

From the Medical Service, AAF Regional Station Hospital, Army Air Base, Richmond, Virginia.

The officer presumably had been in his usual good health until approximately 66 hours prior to admission. During his training, he had successfully passed three of the routine ("type 64") physical examinations given flying personnel. The last of these examinations had taken place five days before admission. Electrocardiographic examinations had not been included.

Three days prior to admission, the pilot had reported for a routine "flight" in the low-pressure chamber. Along with others, including a trained observer, he "ascended" to a simulated height of 18,000 feet without the use of accessory oxygen. This procedure is a routine one to acquaint each flyer with his own reaction to anoxia.\* Constant supervision is maintained. Only the usual mild symptoms were experienced by the patient, i.e., "heavy breathing" and a lack of alertness. No vertigo or visual difficulties were experienced. Individually fitted masks permitting inhalation of 100 per cent oxygen were then applied and used at this altitude for 15 minutes. The group, continuing to breathe pure oxygen, was then taken to a simulated altitude of 38,000 feet.† This elevation was maintained for 16 minutes, during which the subject noted only slight abdominal discomfort. During the "descent," however, he experienced moderate difficulty in adequately ventilating his middle ears, a not unusual symptom. Upon reaching "ground level" the patient felt well except for a slight sensation of blockage of the right ear. There was otoscopic evidence of a mild bilateral aero-otitis media (mild injection of both tympanic membranes, without edema or retraction).

At the termination of the above proceedings, the patient left the base to attend a celebration which lasted throughout the night. Three friends and he consumed two quarts of whiskey and smoked many cigarettes. Returning to quarters at seven the following morning, he felt ill and vomited several times. After four hours of sleep, he awakened conscious of tachycardia, anorexia, and malaise. He remained in or around his quarters all that day and the following day, during which he continued to suffer from malaise and anorexia. He was aware of a rapid pulse rate most of the time. There is no record of the pulse rate or heart rhythm during this period.

On the following day, approximately 60 hours after the completion of the "chamber flight," the patient noted the gradual onset of a "grabbing" sensation in the epigastrium. This was increased by walking and alleviated by resting. Although he was tired, there was no complaint of dyspnea. Upon reporting to his flight surgeon approximately 66 hours after the "flight," he was immediately admitted to the hospital.

On admission the patient was acutely ill and showed moderate perspiration and cyanosis. His respirations were normal in character and the rate was 18 per minute. The pulse was irregular and difficult to count. The blood pressure was determined as 110 mm. Hg systolic and 70 mm. diastolic. The temperature was 98.4° F. Prominent, irregular jugular pulsations were noted, but there were no cardiac pulsations or thrills. The heart was of normal size on clinical and radiologic examination. No murmurs or friction rubs were heard. A totally irregular rhythm was present, and sounds were of poor quality. The cardiac rate, difficult to ascertain, was counted as approximately 150 per minute. A gallop was not detected. There was evidence of marked right-sided heart failure as shown by a tender, non-pulsating, enlarged liver, increased

\* An altitude of 18,000 feet, actual or simulated, represents an atmospheric pressure of 379.4 mm. Hg, or one half the standard pressure at sea level. The partial pressure of oxygen in the atmosphere at this altitude is 79.4 mm. Hg. At 18,000 feet the alveolar oxygen tension of an individual not breathing supplementary oxygen would be approximately 42 mm. Hg; his oxyhemoglobin saturation would be approximately 71 per cent.

† The atmospheric pressure at an altitude of 38,000 feet, actual or simulated, is 154.9 mm. Hg. The partial pressure of oxygen at this altitude is 32.4 mm. Hg. An individual breathing 100 per cent oxygen under these conditions would have an alveolar oxygen tension of 72 mm. Hg; his oxyhemoglobin saturation would be approximately 90 per cent.

venous pressure, and evidence of a small left pleural effusion. No peripheral edema was present.

The following facts pertaining to the past history were elicited later from the patient and his mother: questionable scarlet fever in childhood, frequent sore throats until the age of 12, and several unexplained nose bleeds in 1941. At no time had there been joint pains or chorea. At the age of 15, fainting spells had occurred when the

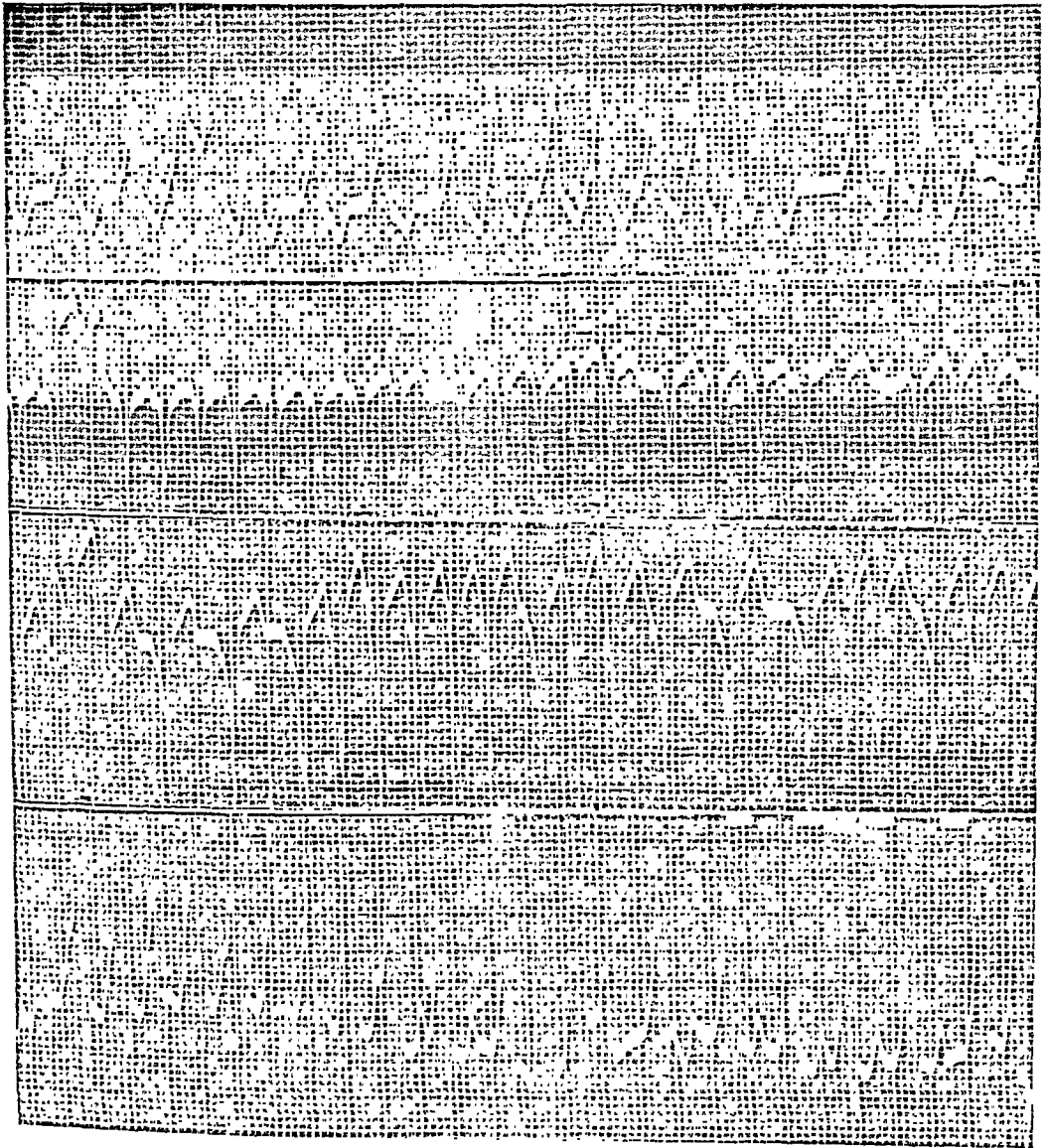


FIG. 1. Initial electrocardiograms, taken within one hour of admission. Ventricular tachycardia, rate varying between 230 and 250.

patient played basketball or football, and on one occasion he had been directed by his doctor to decrease his activities for a week because he had "strained" his heart. No further details of these episodes were available. Both a maternal and a paternal uncle had died of heart disease of unknown types.

*Electrocardiographic Studies and Course.* Figure 1 represents the initial electrocardiogram, taken within an hour of admission. This shows irregular ventricular



tachycardia with a rate varying from 230 to 250. Frequent pauses are noted. In Lead II the slight deflection preceding the main downward deflection is interpreted as part of the QRS complex rather than the P-wave it resembles at first glance. Carotid sinus pressure failed to affect either the rate or rhythm. An electrocardiogram taken one hour later showed no significant changes. (Times identifying the various electrocardiograms are in terms of the 24 hour clock.)

One hour before electrocardiogram 2A was taken a 0.2 gm. test dose of quinidine sulfate had been administered by mouth. This was followed by 0.4 gm. every two hours.

Electrocardiogram 2B, taken after a total dose of 1.0 gm. of quinidine, shows restoration of sinus rhythm, and was the first one showing short PR intervals and wide QRS complexes (Rate 100; PR .10-.12 sec.; QRS .12 sec.). A ventricular premature contraction is seen in Lead CF4.

Only minor variations are noted among tracings 2B, 2C, and 2D. However, in electrocardiogram 2E, taken approximately 17 hours after admission and 13 hours after initiation of quinidine therapy (total dosage 2.6 gm.), a striking change may be observed, i.e., prolongation of PR to .16 sec., diminution of QRS to .08 sec., and inversion of  $T_2$  and  $T_3$ . Five hours later the spontaneous return of the earlier pattern of short PR interval and widened QRS complex was noted (electrocardiogram 2F). At this time quinidine dosage was reduced to 0.2 gm. four times a day and maintained thus until April 25. On March 15 (electrocardiogram 4F) an attempt was made to reduce quinidine to three doses a day but because numerous premature contractions were noted, the dosage was returned to the previous schedule. On May 1 quinidine was discontinued. Electrocardiograms have continued to show the short PR: wide QRS pattern.

Electrocardiograms 3A to 3F demonstrate almost daily variations in the T-waves and a persistence of the short PR: wide QRS pattern, while electrocardiogram 4A (March 9) once more showed the spontaneous occurrence of normal PR intervals and QRS complexes. This electrocardiogram is almost identical with electrocardiogram 2E (March 1). Variations in the configuration of T-waves are noted in electrocardiograms 4B to 4G. Ventricular premature contractions are observed in the last two tracings of this series.

Following subsidence of the ventricular tachycardia, the signs of heart failure diminished markedly within 24 hours. The liver rapidly shrunk in size, and its tenderness disappeared. Within a few days there were no signs of the small pleural effusion.

Shortly before the patient's discharge from the hospital, and at a time when the electrocardiogram showed normal sinus rhythm with the Wolf-Parkinson-White syndrome, carotid sinus pressure produced no changes in the tracing. Subcutaneous and intravenous atropine each effected a decrease in the QRS complex from 0.13 to 0.08 sec.

On the thirty-ninth hospital day, the patient was permitted to sit up in a chair and from that time on his activities were gradually increased. Quinidine was discontinued on the sixty-first day. The patient remained afebrile throughout his entire hospital stay. He was discharged on the eighty-fifth day.

The following laboratory findings are significant. With the exception of a leukocyte count of 10,800 on admission, and one of 9,200 several weeks later, all white counts were from 5,100 to 5,900. The erythrocyte and differential leukocyte counts, as well as hematocrit determinations, were within normal limits. Urinalysis and blood non-protein nitrogen determinations were also normal. Erythrocyte sedimentation rates by the Wintrobe technic were within normal limits (0-3.5 mm. per hr.). The Kahn reaction was negative. All radiologic studies of the chest, including careful fluoroscopy, were negative for evidence of heart disease.

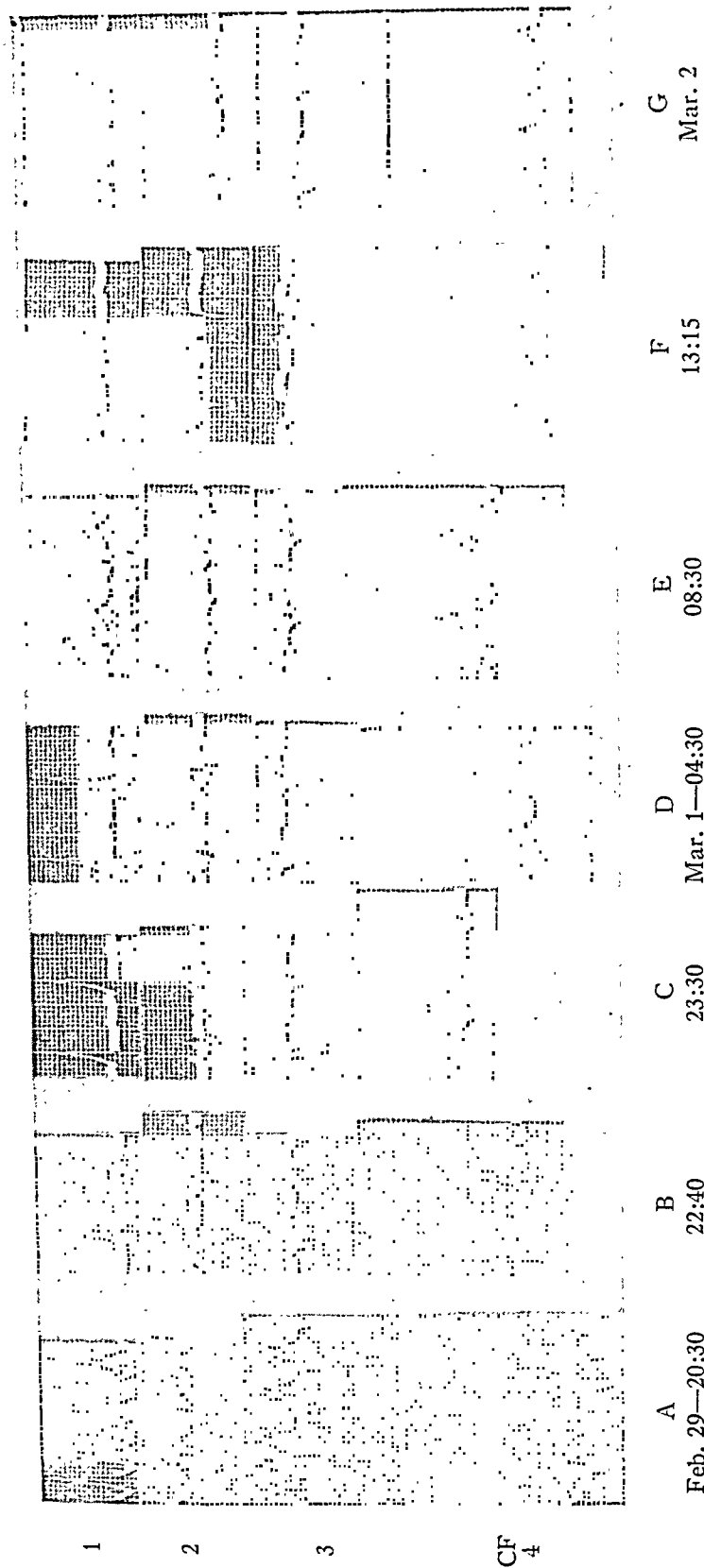


FIG. 2. Tracing A shows no significant change. Note restoration to sinus rhythm, short PR interval and widened QRS complex in B. C and D show only minor differences from B. In tracing E, PR is prolonged to .16 sec. and QRS diminished to .08 sec.; T<sub>2</sub> and T<sub>3</sub> are inverted. Tracings F and G show reversion to short PR and prolonged QRS.



FIG. 3. Persistence of short PR and wide QRS. Striking variation in configuration of T-waves. Note prolonged Q-T interval.



Fig. 4. Spontaneous return to normal PR and QRS. Remainder of tracings show prolonged PR interval, widened QRS complex, and variations in T-waves. Note ventricular premature contractions in tracings F and G.

## DISCUSSION

The authors interpret the arrhythmia as irregular paroxysmal ventricular tachycardia. Because there is some similarity in the form of ventricular complexes before and after cessation of the abnormal rhythm, and because the nature of the auricular rhythm is uncertain, the disturbance also could be interpreted as that of auricular fibrillation with aberration of intraventricular conduction.

Paroxysmal ventricular tachycardia is a disturbance of cardiac rhythm almost invariably associated with serious organic heart disease. The patient described here cannot be said, with any degree of certainty, to have had a normal heart prior to this episode. In addition to the occurrence of fainting spells during adolescence and a family history of heart disease, the history of nose bleeds and frequent sore throats is suggestive of stigmata of rheumatic fever.

Outstanding among the possible precipitating factors leading to the paroxysmal arrhythmia would appear to be the consumption of an inadvisable quantity of alcohol in combination with large amounts of tobacco and loss of sleep. The interval of 14 hours transpiring between the completion of the chamber "flight" and the onset of subjective tachycardia makes it unlikely that exposure to reduced atmospheric pressure contributed significantly to the disturbance of cardiac rhythm.

There does not appear to be sufficient evidence for the diagnosis of myocardial infarction, though for a time this was suspected. T-wave changes of the type seen in these tracings often are observed after prolonged episodes of tachycardia and generally are attributed to anoxemia brought about by the rapid cardiac rate. The persistence of T-wave abnormalities beyond the usual period following the reversion from tachycardia to normal sinus rhythm renders this explanation not entirely unsatisfactory. Though myocardial disturbances of some kind probably were present, accurate delineation of the process is difficult.

The original paper of Wolff, Parkinson, and White<sup>4</sup> presented the syndrome of short PR intervals and widened QRS complexes as occurring in young people with otherwise normal hearts who are subject to attacks of paroxysmal arrhythmia. Hunter et al.,<sup>5</sup> in a series of 22 patients (including three with short PR and normal QRS), presented these interesting facts: a short PR:wide QRS pattern occurred in 5 per cent of 140 consecutive cases of bundle branch block and in about 5 per cent of all patients subject to paroxysmal tachycardia. Although most observers consider that the majority of patients with Wolff-Parkinson-White syndrome have no underlying organic cardiac disease, one must bear in mind that heart disease may be present in some.<sup>6</sup> Eighteen of the 90 cases reviewed by these authors and three of their own 19 patients had organic heart disease. Occasionally the causal connection seems to be definite. In one of their patients the characteristic electrocardiogram occurred soon after rheumatic fever. Examples also have been reported following coronary occlusion.

Even in a patient with associated heart disease, prognosis is usually unaffected by the syndrome, though occasionally patients die during the paroxysms of tachycardia. Where the condition is produced by heart disease, apparently a relatively uncommon happening, the prognosis rests upon the nature and degree of the underlying cardiac lesion. These patients may become seriously ill during

the various arrhythmias. Such was the case with the patient who is the subject of this report.

Although it is not the purpose of this paper to enter into any controversy about the mechanism of the Wolff-Parkinson-White syndrome, a few comments may be offered concerning present day concepts of the condition.

Wolferth and Wood,<sup>9</sup> as well as Holzmänn and Scherf,<sup>10</sup> suggested that the mechanism was ventricular asynchronism with premature stimulation of one ventricle. These authors assumed that the paroxysmal tachycardia was due to retrograde conduction over the Bundle of Kent or a similar structure causing a reentry phenomenon in the auricles, with the production of tachycardia. Such connections have been demonstrated anatomically between the auricles and ventricles,<sup>11</sup> and confirmatory evidence obtains from the careful experiments of Butterworth and Poindexter.<sup>12</sup> By using an amplifier to produce an abnormal pathway between the auricles and ventricles, these workers were able to stimulate one ventricle six to eight hundredths of a second sooner than the other. They were able thereby to produce electrocardiograms comparable to those seen clinically. In addition, these workers were able to produce paroxysmal supra-ventricular tachycardia by reversing the flow of current in the abnormal conduction pathway.

Recognition of the short PR:wide QRS syndrome is not of mere academic interest, since confusion may occur with true bundle branch block or with myocardial infarction. The syndrome is characterized by upright P-waves when the rate is normal, abolition of the isoelectric segment from P to R, and reduction of the PR interval to 0.12 sec. or less. The ventricular complex resembles that of bundle branch block. It is widened beyond 0.10 sec. and often slurred in its ascent and notched near its summit. The RT period may be depressed or elevated, seldom assuming the full diphasic characteristic of ordinary bundle branch block. There also is a tendency for the PT interval (beginning of the P-wave to the end of the QRS complex) to remain constant when normal and abnormal complexes are compared in the same person.

Another interesting feature is that the same patient may show abnormal complexes on one occasion and normal ones on another, the rate being normal on both occasions.<sup>14</sup> Such changes may occur spontaneously or may be induced by exercise or atropine.

#### SUMMARY

A case of irregular paroxysmal ventricular tachycardia associated with short PR intervals and wide QRS complexes (Wolff-Parkinson-White syndrome) is reported. During the arrhythmia, the patient developed signs of right heart failure. Quinidine produced an excellent therapeutic response. Pertinent literature is discussed.

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## A CASE OF SHORT PR INTERVAL AND PROLONGED QRS COMPLEX WITH A PAROXYSM OF VENTRICULAR TACHYCARDIA \*

By MAX J. KLAINER, Captain, M.C., A.U.S., *Stoneham, Massachusetts*, and  
HAROLD H. JOFFE, Captain, M.C., A.U.S., *Duluth, Minnesota*

IN 1930 Wolff, Parkinson and White called attention to a syndrome of "bundle branch block with short PR interval" occurring in healthy young people who were prone to recurrent attacks of paroxysmal auricular tachycardia or auricular fibrillation.<sup>1</sup> In recent years this syndrome has been recognized with increasing frequency and it has been established that this was not a bundle branch block, but the manifestation of an early arrival in the ventricle of the auricular impulse through an accessory pathway, the bundle of Kent.<sup>2, 3</sup> In 1941 Levine and Beeson called attention to the fact that this syndrome could also be associated with paroxysms of ventricular tachycardia.<sup>4</sup> They commented that only two such cases had been previously reported and added three more. A further review of the literature on this subject failed to reveal any additional cases. The purpose of this paper is to add one more case to this small series.

\* Received for publication May 5, 1945.

## CASE REPORT

A 29 year old white male with one month of military service was admitted to the Regional Hospital, Fort Riley, Kansas, on February 10, 1945, complaining of rapid irregular heart action. Past history revealed that since the age of 19 this patient had been subject to recurrent bouts of this nature. He had had about 18 such attacks which were from one to five days in duration. At the age of 20 he was kept in bed for six weeks following such an attack. In June 1944 an electrocardiogram was taken during a paroxysm of tachycardia and he was treated with quinidine. The onset of each episode was sudden and was accompanied by vertigo, dyspnea and an aching

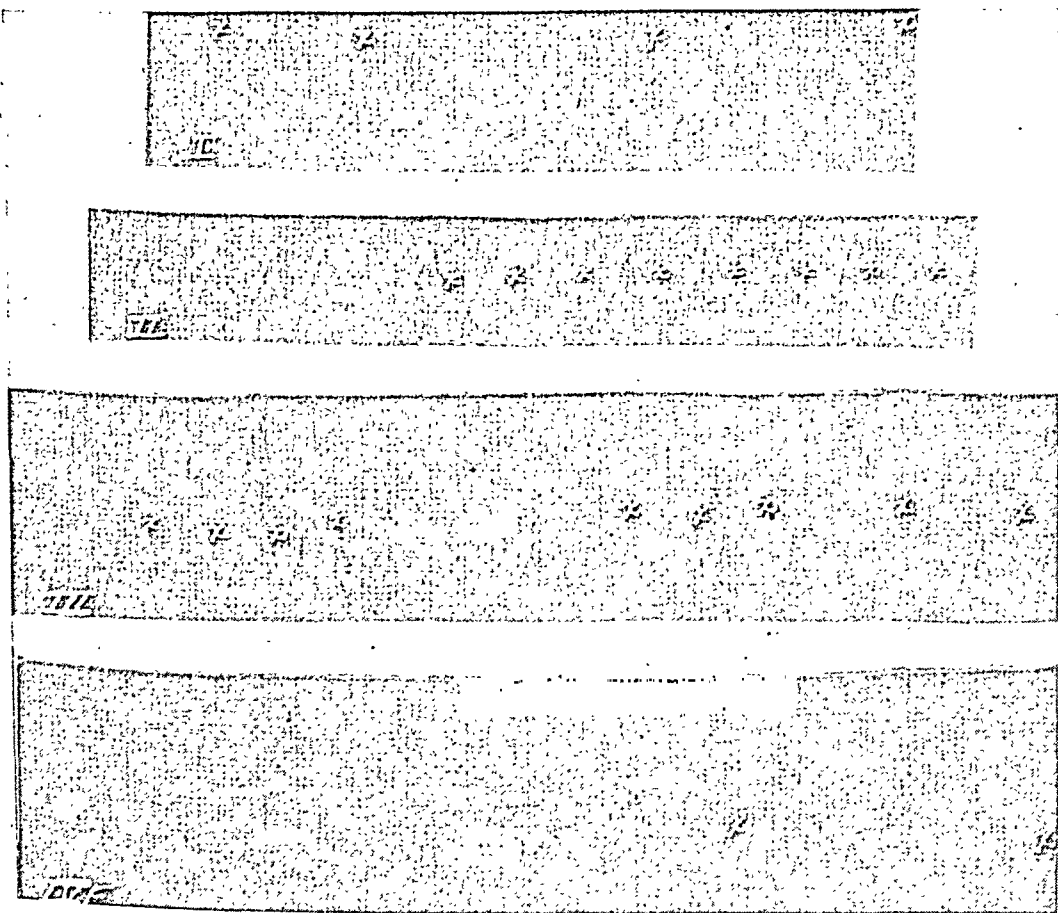


FIG. 1. Electrocardiogram taken on admission during the paroxysm of tachycardia and interpreted as ventricular tachycardia. The QRS complexes are slurred and widened in all leads with a maximum duration of 0.16 second. The ventricular rate is 150 beats per minute. The T-waves are opposite the main deflection in all leads. There are occasional supraventricular beats. The auricular rate cannot be determined but in all the leads there is superimposed notching on various phases of the QRST complex (indicated by x marks) which could be the result of auricular contractions.

sensation in the lower left anterior chest. The offset of these attacks tended to be gradual. Except for a period of weakness of a few days' duration following each bout of tachycardia he felt well between attacks and was able to perform the work of a machinist in civilian life. The family history was negative except for bronchial asthma in one brother.

Physical examination on admission revealed a well developed and well nourished



have been reported in which no organic heart disease could be found.<sup>5, 6</sup> Williams and Ellis<sup>5</sup> divided their series of 36 cases of ventricular tachycardia into two types—the persistent and the intermittent. The latter were characterized by runs of ventricular tachycardia separated by periods of normal rhythm. We feel that the tachycardia seen in this case is of the intermittent type. In figure 1, Leads II, III and IV, there are runs of ventricular tachycardia separated by an occasional supraventricular beat. Furthermore, in this tracing it is possible to detect superimposed notching on various phases of the QRST complex which could represent either an independently beating auricle or retrograde conduction

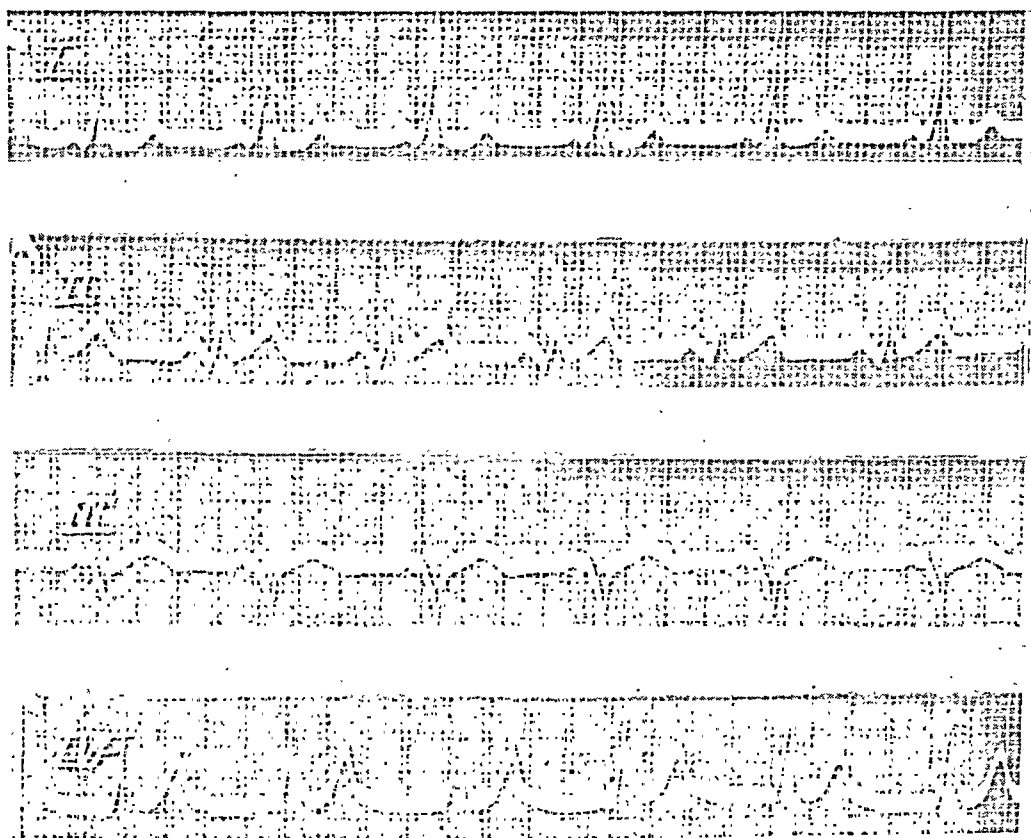


FIG. 4. Electrocardiogram taken 20 minutes after the administration of 2 c.c. of prostigmine methylsalicylate intramuscularly. The QRS complex is somewhat more widened, measuring up to 0.14 second, but is otherwise unaltered. The PR interval is unchanged.

from the ventricle to the auricle. Although a supraventricular tachycardia can produce anomalous ventricular complexes which may simulate those of a ventricular paroxysm, we feel that the tracing obtained in this case more closely resembles that of a true ventricular tachycardia.

This case unquestionably satisfies all the criteria of the Wolff, Parkinson and White syndrome, namely: the short PR interval, the prolonged QRS complexes, initial slurring of the QRS complexes, and paroxysmal attacks of tachycardia. Studies of the effect of various drugs on the electrocardiogram of this patient confirm the results previously reported by other investigators.<sup>7, 8</sup> Atropine shortened the QRS complexes which assumed a more normal contour, whereas

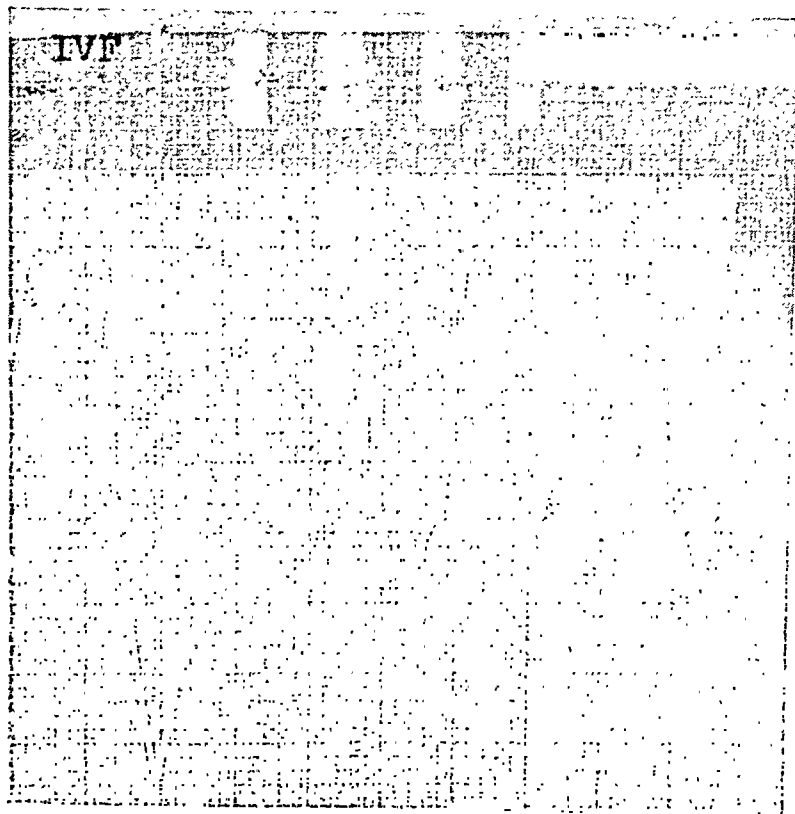
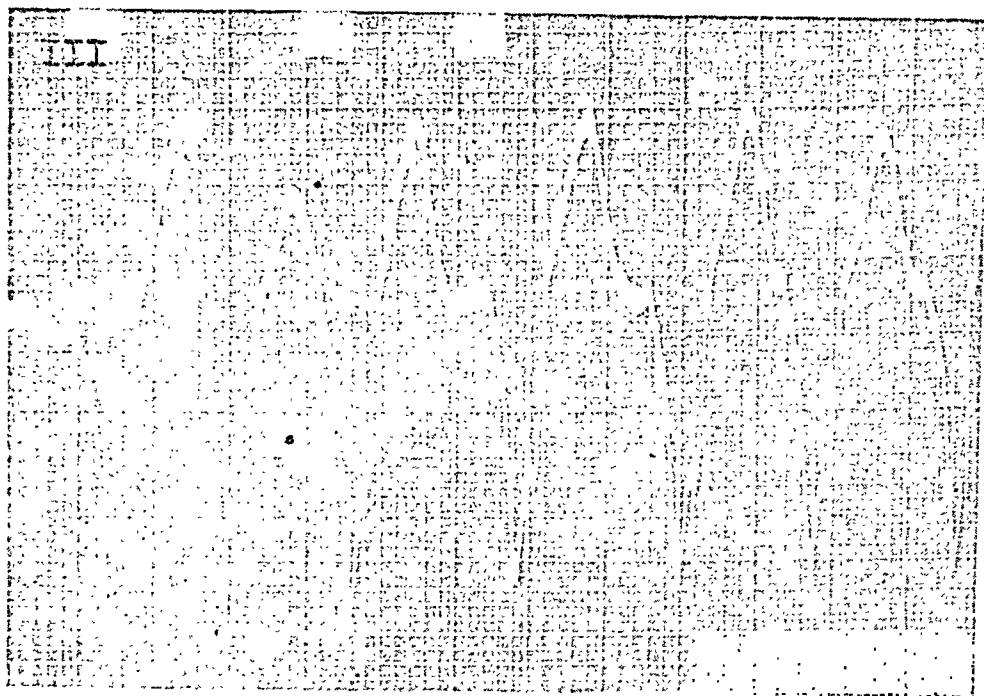


FIG. 5. Portion of electrocardiogram (Leads III and IV F) taken in June 1944 during a paroxysm of tachycardia. This is also a ventricular type of tachycardia and further supports our belief that this arrhythmia in this case is related to the other peculiarities of the conduction system seen in the Wolff-Parkinson-White syndrome.

prostimine produced widening of these complexes. No changes were noted after digitalis medication, but it is possible that the amount of the drug given may have been insufficient to produce any effect.

The occurrence of paroxysmal ventricular tachycardia and the syndrome of short PR interval and prolonged QRS complex together may be coincidental. As mentioned previously such paroxysms have been reported in structurally normal hearts. In these cases, however, electrocardiograms taken during periods of normal rhythm have usually shown one or more irritable foci in the ventricles as evidenced by ventricular extrasystoles. In the case reported we were unable to demonstrate any structural defect of the heart, and none of the numerous electrocardiograms taken after normal rhythm was established showed any ventricular extrasystoles. Furthermore, none was seen after the patient was given sizeable doses of digitalis. Therefore, we are of the opinion that the paroxysm of ventricular tachycardia seen in this case is not coincidental but is related to the other peculiarities of the conduction system seen in the Wolff-Parkinson-White syndrome (see figure 5). At the present time it is not possible to postulate a mechanism whereby the ventricles can set up a dominant idioventricular rhythm, but it could possibly be related to the theory proposed by Wolferth and Wood<sup>9</sup> as an explanation for the paroxysms of auricular tachycardia seen in this syndrome. These investigators suggested that retrograde conduction from ventricle to auricle through the bundle of Kent could set up the auricular arrhythmia. Butterworth and Poindexter,<sup>10</sup> in 1942, presented an experimental study on cats and dogs which supported this theory. They showed that by the use of an abnormal electrical conducting pathway it was possible to produce typical electrocardiographic tracings with a short PR interval and a prolonged QRS complex. By reversing the flow of electrical stimulation from ventricle to auricle typical paroxysms of auricular tachycardia were produced. The case here reported may lend support to the theory of retrograde conduction from ventricle to auricle. Figure 1 reveals waves superimposed on the QRST complexes which could represent auricular contractions of this nature.

#### SUMMARY

1. A case of short PR interval with prolonged QRS complex observed during a paroxysm of ventricular tachycardia has been reported, bringing the total of such reported cases to six.

2. The mechanism whereby the ventricle can set up a dominant idioventricular rhythm in this syndrome is unknown, but it could be related to the theory of retrograde conduction from ventricle to auricle through the bundle of Kent.

3. The appearance of the electrocardiogram during the paroxysm of the ventricular tachycardia may lend support to the theory of retrograde conduction as a cause for the paroxysms of tachycardia seen in this syndrome.

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## EDITORIAL

### *IMMUNIZATION WITH PNEUMOCOCCUS POLYSACCHARIDE*

DURING the past thirty years many studies on prophylactic immunization against pneumococcal pneumonia have been made with a number of different antigenic preparations. Among the earliest of these studies was that of Cecil and Austin<sup>1</sup> who tested the effect of prophylactic vaccination against pneumococcal pneumonia at Camp Upton, New York, in 1918. Their vaccine consisted of a saline suspension of heat-killed pneumococci types I, II, and III. Almost all investigators have concluded that immunization exerts a beneficial effect. In most of the studies, however, interpretation of the results was clouded by such variables as differences in the composition of the immunized and control groups; uncertainty as to whether the specific pneumococcal types included in the immunizing preparation were the same as those currently causing pneumonia; failure to determine whether the observed decline in cases in the immunized group was due to a decrease in cases caused by pneumococcal types included in the vaccine; and inadequate control of the antigenicity of the preparations used.

It has been repeatedly demonstrated that animals can be protected against infection by virulent pneumococci by means of antibodies directed against the specific capsular polysaccharides. Francis and Tillett<sup>2</sup> were the first to show that the purified capsular polysaccharides of pneumococci are antigenic for man when injected intracutaneously in a single dose as small as 0.01 milligram. Subsequent immunization projects by various investigators in mental institutions and civilian camps furnished highly suggestive evidence that these polysaccharides may be used successfully to protect human beings against the corresponding types of pneumococcal pneumonia. It remained, however, for MacLeod, Hodges, Heidelberger, and Bernhard<sup>3</sup> to present incontrovertible evidence of the efficacy of such immunization in their perfectly beautiful clinical experiment completed less than one year ago.

The conditions under which MacLeod and his associates carried out their project were as close to ideal as is conceivable. They felt, therefore, that the important sources of error in such a study had been eliminated and that consequently the interpretation of the results could be made with more assurance than had been previously possible. The population chosen was that of a large Army Air Force Technical School, where during the two preceding winters high epidemic rates for pneumococcal pneumonia had prevailed. Information on the serologic types of pneumococci identified from the 1500

<sup>1</sup> CECIL, R. J., and AUSTIN, J. H.: Results of prophylactic inoculation against pneumococcus in 12,519 men, *Jr. Exper. Med.*, 1918, xxviii, 19-41.

<sup>2</sup> FRANCIS, T., JR., and TILLET, W. S.: Cutaneous reactions in pneumonia; development of antibodies following intradermal injection of type-specific polysaccharide, *Jr. Exper. Med.*, 1930, lii, 573-585.

<sup>3</sup> MACLEOD, C. M., HODGES, R. G., HEIDELBERGER, M., and BERNHARD, W. G.: Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides, *Jr. Exper. Med.*, 1945, lxxxii, 445-465.

cases of pneumonia occurring in the first two years was available. Types II, I, V, VII, XII, and IV, in that order, caused 75 per cent of the cases of disease, the rates for the individual types being approximately the same for each of the two years. The living conditions and duties of the population, which had been remarkably uniform during the 1942-43 and 1943-44 seasons, were unchanged during the season 1944-45. A reasonable prediction could thus be made that the incidence of pneumococcal pneumonia during the experimental period would be high and also what types of pneumococci would be involved. Accordingly, the solution used for immunization contained the specific capsular polysaccharides of pneumococcus types I, II, V, and VII; types XII and IV remained as controls. The preparations of polysaccharides were of known antigenic potency as determined previously by inoculation of civilian volunteers.

Immunization by a single subcutaneous injection of the polysaccharides (0.03 to 0.06 milligram of each) was carried out on alternate members of the population, thus insuring a thorough mixing of immunized and non-immunized subjects in all phases of their activities. Computation of the man-days of exposure gave approximately equal values for the two groups. Furthermore, the members of the population could be observed for a reasonably long time, since the students remained at the school for twenty-four weeks. Laboratory facilities were available for typing all cases of pneumonia and, in addition, a continuous carrier survey for pneumococci was carried on, the total sample being over 3700 pharyngeal cultures with an over-all pneumococcal carrier rate of 57.7 per cent.

The evidence obtained by MacLeod and his associates demonstrated clearly that immunization of man with the specific capsular polysaccharides of pneumococcus types I, II, V, and VII is effective in preventing the development of pneumonia due to these types in the immunized subjects. Of equal interest was the observation that immunization of half the population against those four types greatly reduced the incidence of pneumonia due to these types in the non-immunized subjects, the observed incidence of type I, II, V, and VII pneumonia in the non-immunized fraction of the population being but 17.6 per cent of the expected. This conclusion was based on the observed behavior of type XII and type IV in that for each of these types the rates of pneumonia were closely similar for the 1942-43, 1943-44, and 1944-45 seasons.

Earlier studies by other investigators had shown that when pneumococcal pneumonia is epidemic the carrier rates for the epidemic types were high. The same was shown to be true for pneumococcus type XII in MacLeod's study. It seemed probable that the failure of the non-immunized portion of the population to develop high pneumonia rates was due to inhibition of the development of high carrier rates for type I, II, V, and VII as a consequence of its being thoroughly mixed with the immunized portion. In this regard, evidence was presented that the carrier rates for these types in the immunized portion of the population were significantly lower than

in the non-immunized. It was further stressed that the elimination of pneumonia cases in half the population should bring about a comparable elimination of case-contact carriers. For these reasons, it was suggested that the ability of the immunized subjects to carry and disseminate types I, II, V, and VII pneumococci was greatly reduced by specific immunity to these types and that this immune barrier, composed by half the population, greatly reduced the dissemination of these types throughout the whole population.

The time required for the development of immunity following injection of the polysaccharides was believed to be in the neighborhood of two weeks, based on the observation that the only cases of pneumonia among the immunized men that were caused by types I, II, V, or VII developed during the first two weeks after immunization. In support of this conclusion, studies on the serum of immunized individuals showed that specific antibodies developed within this time but usually required three to six weeks to reach their maximum. The duration of immunity was not determined, but it was apparent that six months could be set as a minimum.

Because of the relatively low incidence of pneumococcal pneumonia in civilian populations, antipneumococcal immunization is unlikely to become a general procedure. In certain groups of greater risk such as foundry workers, miners, and inmates of mental institutions, however, immunization would seem to be a desirable procedure. In military populations the greatest incidence of pneumonia occurs in new recruits, so that most benefit would be derived from immunization of this group.

MacLeod and his associates are surely to be congratulated on their carefully controlled piece of clinical research, carried out on a scale sufficiently large to render their conclusions statistically valid. Their study might well be held up as a model for future immunization projects.

W. H. B.

## REVIEWS

*Physical Chemistry of Cells and Tissues.* By RUDOLF HÖBER, University of Pennsylvania School of Medicine, Philadelphia, Pa., with the collaboration of DAVID I. HITCHCOCK, Yale University School of Medicine, New Haven, Conn., J. R. BATEMAN, Mayo Clinic, Rochester, Minn., DAVID R. GODDARD, University of Rochester, Biological Laboratories, Rochester, Minn., and WALLACE O. FENN, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. The Blakiston Company, Philadelphia. 676 pages; 23.5 × 16 cm. 1945. Price, \$9.00.

Physiology is presented from the point of view of physical science in "The Physical Chemistry of Cells and Tissues." In so doing the authors have done much to bridge some of the gaps between some of the concepts of biological and physical science.

The first section consists of a survey of the fundamentals of physical chemistry which presupposes a basic knowledge in this field. In the second section, Dr. Bateman discusses the architectural and functional significance of large molecules in living matter. The contents of the following five chapters are reflected in their titles: Inter-atomic and Intermolecular Forces; Some Properties of Large Molecules in Solution; Condensed Systems of Large Molecules with Special Reference to the Structure of Fibers; and Some Properties of Films and Membranes.

Dr. Höber has written the next three sections. The first, introductory in nature, presents some of physiochemical properties of protoplasm which are important in the consideration of protoplasm as the basic substance of living matter. Subsequent chapters deal with the properties of the protoplast and the influence of environment (both natural and experimental) upon its permeability and upon its various metabolic activities.

The author is an authority in this field, having spent many years in the study of cell permeability and the effects of environment upon cell potential, permeability to electrolytes, to non electrolytes and upon activity. He has succeeded in correlating much of the significant material and has raised questions which must still be answered. Dr. Höber again takes up the problem of permeability in section 8, following a discussion by Dr. Fenn of the contractility of tissue. This section is concerned primarily with physiological permeability and includes various phases of intestinal absorption and urine formation and the elaboration of digestive secretions.

Dr. Goddard has written an excellent review of respiration in cells and tissue which includes a chapter on respiratory enzymes and the various cycles which may be involved in the stepwise degradation of carbohydrates with the liberation of energy. The volume is an outstanding contribution to biological science.

M. A. A.

*Clinical Atlas of Blood Diseases. Sixth Edition.* By A. PINEY, M.D., M.R.C.P., and STANLEY WYARD, M.D., F.R.C.P. 138 pages; 20.5 × 13.5 cm. 148 illustrations. 1945. Blakiston Co., Philadelphia. Price, \$5.00.

Many people have received help from this little volume. This is the sixth edition. The illustrations are excellent and the text terse and informative. It can be recommended for ready reference.

T. P. S.



## BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Textbook of General Surgery.* By WARREN H. COLE, M.D., F.A.C.S., and ROBERT ELMAN, M.D. Fourth Edition. 1118 pages; 24 × 16.5 cm. 1944. D. Appleton-Century Company, New York.

*Science and Seizures.* By WILLIAM GORDON LENNOX, M.D., Sc. D. Hon. Second Edition. 258 pages; 20 × 12 cm. 1946. Harper & Brothers, New York. Price, \$2.00.

*Alterações Hepáticas na Tirotoxicose.* By P. A. DA COSTA COÛTO, Clínico do Instituto dos Bancários. 278 pages; 23.5 × 16 cm. 1944. Borsoi, Rio de Janeiro.

*Ambulatory Proctology.* By ALFRED J. CANTOR, M.D. 524 pages; 24.5 × 16 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$8.00.

*Applied Physiology.* By SAMSON WRIGHT, M.D., F.R.C.P. 944 pages; 22.5 × 14.5 cm. 1945. Oxford University Press, New York. Price, \$9.00.

*The Diagnosis of Nervous Diseases.* By Sir JAMES PURVES-STEWART, K.C.M.G., C.B. Ninth Edition. 880 pages; 22 × 14.5 cm. 1945. Williams & Wilkins Company, Baltimore. Price, \$11.00.

*Skin Diseases in Children.* By GEORGE M. MACKEE, M.D., and ANTHONY C. CIPOLLARO, M. D. Second Edition Revised and Enlarged. 448 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. Price, \$7.50.

*Tratado de Cardioangiologia.* By PEDRO A. TAPELLA. Docente Libre de Patologia Medica en la Facultad de Buenos Aires. 946 pages; 27 × 18 cm. 1946. Lopez & Etchegoyen S.R.L., Buenos Aires.

*Tratado de Patologia Medica.* By DR. RODOLFO DASSEN, DR. E. G. FONGI, and DR. O. FUSTINONI. 819 pages; 27 × 18 cm. 1946. Lopez & Etchegoyen S.R.L., Buenos Aires.

*Bulletin de L'Académie Suisse des Sciences Médicales.* Vol. 1, 1944. FASC 1 & 2. 120 pages. 24 × 16 cm. Benno Schwabe & Co., Basel.

*Asma Alergia.* By DR. GUIDO RUIZ MORENO. 186 pages; 22.5 × 15 cm. 1946. Lopez & Etchegoyen, S.R.L., Buenos Aires.

*Seleções Médicas do Brasil.* Fundação E. Direção Do Professor Nuno Lisboa. 1945. 116 pages; 23 × 16 cm.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS OF THE COLLEGE

The College is gratified to announce the following additional Life Members, listed in the order of subscription:

Dr. Lawrence Arthur Williams, F.A.C.P., Pasadena, Calif.  
Dr. Virgil Guy Presson, F.A.C.P., Tucson, Ariz.  
Dr. Alfred Winfield Dubbs, F.A.C.P., Allentown, Pa.  
Dr. Gertrude Mary Engbring, F.A.C.P., Chicago, Ill.  
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.  
Dr. Robert Stanley Flinn, F.A.C.P., Phoenix, Ariz.  
Dr. John Joseph Dumphy, F.A.C.P., Worcester, Mass.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged.

Lewis H. Bronstein, (Associate), Fort George Meade, Md.—5 reprints  
C. T. Burnett, F.A.C.P., Denver, Colo.—1 reprint  
Arthur C. Clasen, F.A.C.P., Seattle, Wash.—1 reprint  
Norbert Enzer, F.A.C.P., Milwaukee, Wis.—13 reprints  
M. B. Guthrie, (Associate), Fort McPherson, Ga.—1 reprint  
Sydney Jacobs, F.A.C.P., New Orleans, La.—7 reprints  
Arthur L. Kruger, F.A.C.P., Norfolk, Va.—1 reprint  
John E. Leach, F.A.C.P., New York, N. Y.—1 reprint  
D. O. N. Lindberg, F.A.C.P., Wabasha, Minn.—1 reprint  
J. F. McManus, F.A.C.P., Waltham, Mass.—1 reprint  
Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—2 reprints  
Richard Reeser, Jr., F.A.C.P., St. Petersburg, Fla.—1 reprint  
William S. Reveno, F.A.C.P., Detroit, Mich.—2 reprints  
H. C. Robinson, F.A.C.P., Grand Rapids, Mich.—1 reprint  
J. B. Schwedel, F.A.C.P., New York, N. Y.—10 reprints  
Maurice S. Segal, F.A.C.P., Boston, Mass.—1 reprint  
Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint

The College Headquarters acknowledges with thanks to the author, Dr. Peter J. Steincrohn, F.A.C.P., Hartford, Conn., one copy of his book entitled "Angina Pectoris and Coronary Occlusion," which has been added to the College library.

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### NORTH CAROLINA REGIONAL MEETING

The annual regional meeting of the College for the State of North Carolina will be held at the Bowman Gray School of Medicine at Winston-Salem October 18, 1946.

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### A.C.P. REGIONAL MEETING FOR MONTANA AND WYOMING

Under the Governorship of Dr. Ernest D. Hitchcock, of Great Falls, Montana, a Regional Meeting of the American College of Physicians was held at Billings, Montana, April 27, 1946, for the states of Montana and Wyoming. In addition to

the program listed below, there was a Business Session and a Dinner at the Northern Hotel.

The program consisted of the following:

Rocky Mountain Spotted Fever in Eastern Montana,  
Malcolm D. Winter, M.D., F.A.C.P., Miles City.

Symposium on Chronic Bronchitis and Related Conditions:

1. Perennial Asthma with Emphasis on Intrinsic Asthma,  
Maurice A. Shillington, M.D., F.A.C.P., Glendive;
2. Pathogenesis of Pulmonary Fibrosis and Emphysema,  
Harold W. Gregg, M.D., F.A.C.P., Butte;
3. Management of the Bronchiectatic Patient,  
Keith D. Larson, M.D., Billings (by invitation);
4. Cor Pulmonale,  
Ferdinand R. Schemm, M.D., F.A.C.P., Great Falls.

The Murray-Wagner-Dingle Bill,  
Allen R. Foss, M.D., F.A.C.P., Missoula.

Rheumatic Fever in Children,  
Archie L. Gleason, M.D., F.A.C.P., Great Falls.

Massive Hemorrhage from the Upper Digestive Tract,  
W. W. Arrasmith, M.D., F.A.C.P., Casper.

Sufficient time was allotted for discussion of each paper from the floor.

#### A.C.P. COURSE IN INTERNAL MEDICINE AT THE UNIVERSITY OF CALIFORNIA

The Medical Faculty of the University of California will give a course in Internal Medicine at the Medical Center, San Francisco, from June 17-28, inclusive, under the sponsorship of the American College of Physicians and as part of its postgraduate program. Dr. Stacy R. Mettier, Associate Professor of Medicine and Chairman of the Committee on Postgraduate Instruction, will direct the course. Sessions are scheduled daily, five days a week, Monday through Friday, from 9:00 a.m. to 5:00 p.m. Symposia will be given on:

ENDOCRINOLOGY; GOITER; THE ANEMIAS; PSYCHOSOMATIC RELATIONSHIPS; PULMONARY DISEASES; NUTRITION; PEPTIC ULCER; ULCERATIVE COLITIS; GALL BLADDER DISEASES; ARTHRITIS; AMEBIASIS; MEDICAL AND OBSTETRICAL PROBLEMS OF INTEREST TO THE INTERNIST; HEART DISEASE; DISEASES OF THE LIVER; NEUROLOGY; INFECTIOUS DISEASES; SYPHILIS; LOW BACK PAIN.

Full details have been published in the postgraduate bulletin of the American College of Physicians. Fees for the course are as follows:

|                                                     |         |
|-----------------------------------------------------|---------|
| Members of the American College of Physicians . . . | \$40.00 |
| Non-members . . . . .                               | 80.00   |

The American College of Physicians is unable to provide veteran medical officers, members or non-members of the College, the benefits of the amended G. I. Bill of Rights, through which the Veterans Administration pays tuition fees. The College has not the administrative machinery to comply with the regulations through which collections must be made through the Veterans Administration. This course occurs during the two weeks preceding the opening of the American Medical Association meeting in San Francisco. Adequate hotel accommodations have been engaged

through the instrumentality of Dr. Mettier to accommodate all registrants in this course; up to a limit of 150.

For detailed program and application form, address the Educational Director, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

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#### A.C.P. ASSOCIATES SHOULD ATTEND ANNUAL SESSIONS OF THE COLLEGE

Associates of the College are expected to show an interest in College activities and in the postgraduate facilities offered by the College. Attendance at the Annual Sessions is recorded on the records of every Associate and Fellow of the College. The Credentials Committee anticipates that every Associate, now that the war is over, will attend at least one Annual Session before he comes up for advancement to Fellowship. Associates were excused from this during World War II, first, because many were on military duty; second, because the College had to discontinue its Annual Sessions after 1942.

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Dr. Arthur O. Hecker, F.A.C.P., formerly of Harrisburg, Pa., has been appointed Clinical Director of the Veterans Administration Hospital, Coatesville, Pa., effective March 5, 1946.

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Dr. Benjamin L. Brock, F.A.C.P., formerly of Waverly Hills Sanatorium, Waverly Hills, Kentucky, has been appointed Clinical Director of the Veterans Administration Hospital, Oteen, N. C.

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Dr. Mitchell Bernstein, F.A.C.P., and Dr. Hyman I. Goldstein, Associate, of Camden, N. J., addressed the Northern Medical Association of Philadelphia on March 21, 1946.

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Dr. W. P. Anderton, F.A.C.P., New York City, has been appointed Consultant in Medicine to the Flushing Hospital and Dispensary, Flushing, L. I., N. Y.

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Dr. Cyril M. MacBryde, F.A.C.P., who has been on the staff of the Washington University School of Medicine since 1933, has moved to Los Angeles and has joined the faculty of the University of Southern California Medical School where he will be Assistant Professor of Clinical Medicine. He will be in charge of the Endocrine Clinic at the Los Angeles County General Hospital. Dr. MacBryde will practice internal medicine in association with the Shelton Clinic, 921 Westwood Boulevard, Los Angeles, and will continue his investigative work on improved forms of insulin and other metabolic and endocrine subjects.

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Dr. Francis Gilman Blake, F.A.C.P., Regent of the American College of Physicians, and President of the Army Epidemiological Board, received the Medal of Merit from Major General Norman T. Kirk, F.A.C.P., Surgeon General of the Army, for his outstanding work in planning and organizing the Army Epidemiological Board and as Consultant to the Secretary of War.

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Dr. Clarence de la Chapelle, F.A.C.P., Director of the Postgraduate Division of New York University College of Medicine, recently stated that 400 medical veterans have attended postgraduate courses organized by his Division in September 1945.

Dr. William Harvey Perkins, F.A.C.P., Dr. Edward L. Bortz, F.A.C.P., Dr. George Morris Piersol, F.A.C.P., and Dr. William G. Leaman, Jr., F.A.C.P.; all of Philadelphia, recently spoke before the Sixteenth Annual Health Institute of the Woman's Auxiliary to the Philadelphia County Medical Society.

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Dr. Max Pinner, F.A.C.P., formerly Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons, and Chief of the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York City, has removed to 463 Vermont Ave., Berkeley, Calif., and has discontinued the private practice of medicine. His time will be devoted to the editorship of the American Review of Tuberculosis.

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Major Rafael Rodriguez-Molina, Medical Corps, F.A.C.P., has been awarded the Army Commendation Ribbon for commendable service from May 22, 1942 to February 12, 1946 as Assistant Chief and Chief of the Medical Service, 161st General Hospital, A.P.O. 851, U. S. Army.

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Dr. Anthony Bassler, F.A.C.P., of New York City has been selected as Vice-President of the International Gastroenterologic Society and President of the permanent International Committee of the organization.

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An important forward step in the establishment of professional graduate training for Army doctors has been taken with the enactment of the new Army Regulation 350-1010, which authorizes the establishment of an organized program of graduate education for "the elevation of the general level of professional qualifications of all Medical Corps officers." The Surgeon General assisted by the professional consultants in the various specialties will exercise overall organization and supervision of the program of graduate education in the Army Medical Corps. The objectives are numerous, and include provision for adequate training and qualification of professional and administrative specialists, ample opportunities for professional advancement in clinical and research medicine, establishment of all Army Hospitals as teaching institutions, and finally, to develop the art and science of medicine and to encourage continuous postgraduate medical teaching and education.

This organized program will be carried out in consecutive steps by means of Army internships, mixed residencies, residencies in medical and surgical subspecialties, postgraduate subspecialty training, and projects in military medical research. Training in the basic medical sciences will be conducted concurrently with other phases of this program.

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The chief medical director of the Veterans Administration, Brigadier General Paul R. Hawley, recently announced from Washington the following appointments:

Dr. Charles C. Wolferth, F.A.C.P., University of Pennsylvania Hospital, chief of the cardiology section of the Veterans Administration's Professional Services Division.

Dr. Albert M. Snell, F.A.C.P., Mayo Clinic, chief of the gastro-enterology section.

Brig. Gen. James S. Simmons, F.A.C.P., Boston, Army Medical Corps, chief of tropical medicine.

Dr. Harry L. Alexander, F.A.C.P., Barnes Hospital, St. Louis, chief of allergy.  
Dr. Richard A. Kern, F.A.C.P., University of Pennsylvania Hospital, chief consulting internist.

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The Nineteenth Graduate Fortnight of the New York Academy of Medicine will be held during the dates October 7 and 18, 1946, on the subject of Tumors. The Fortnight will include Evening Lectures, Morning Panel Discussions, Scientific Exhibits and demonstrations at the Academy; and Afternoon Hospital Clinics at leading hospitals of New York City.

Physicians, who are not Fellows of the Academy, may secure registration by sending name and address, accompanied by check for five dollars, to the Secretary of the Graduate Fortnight Committee, 2 East 103rd Street, New York 29, New York.

Medical Officers of the Army, Navy and United States Public Health Service, on active duty, will be admitted to all sessions without registration fee.

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Fellowships for one year of graduate study in health education, leading to a master's degree in public health, are being offered to qualified men and women by the U. S. Public Health Service through funds made available by the National Foundation for Infantile Paralysis, according to a recent release from the Federal Security Agency of the U. S. Public Health Service, Washington 25, D. C.

These fellowships provide a stipend of \$100 a month in addition to tuition and travel expenses for the entire period of academic and field training starting in the fall of 1946. Persons accepting fellowships will be expected to work in the field of health education for at least two years after completion of training. Applications may be secured from the Office of the Surgeon General, U. S. Public Health Service, Washington 25, D. C., and should be returned thereto not later than June 1, 1946.

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The annual intensive course in Electrocardiography for graduate physicians will be given at Michael Reese Hospital in Chicago from August 19-31, 1946. The Director is Dr. Louis N. Katz, F.A.C.P. Applications should be made to the Cardiovascular Department of the Michael Reese Hospital, 29th Street & Ellis Avenue, Chicago 16, Ill.

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Dr. Joseph R. Ridlon, F.A.C.P., a Medical Director in the U. S. Public Health Service, has recently been retired and will be located in Gorham, Maine.

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In July 1942 Capt. Robert Gaylord Davis, (MC) USN, F.A.C.P., was reported "missing in action" and for almost the duration of the war was thought to have been dead. However, he was found in a Japanese Prisoner of War Camp and liberated in August 1945 and returned to the United States during September. Following a period of hospitalization and rehabilitation leave, Capt. Davis was assigned again to active duty. However, he is scheduled for detachment to pre-retirement leave and will be officially retired on August 1, 1946.

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Capt. Lyle Jay Roberts, (MC) USN, F.A.C.P., was taken prisoner by the Japanese in the early part of the war, but liberated during September 1945 and returned to the United States in October. Following a period of hospitalization, he was granted a rehabilitation leave and has now reported for active duty again.

Dr. James E. Cottrell, F.A.C.P., formerly of Philadelphia, was separated from the Medical Corps of the Army during March 1946, and has accepted a full time position in the Veterans Administration as Chief of the Medical Service in the Veterans Hospital, Memphis, Tenn.

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Dr. Chester S. Keefer, F.A.C.P., Boston, and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, recently addressed the Connecticut State Medical Society at its 154th meeting in Hartford, Conn.

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Dr. William S. Middleton, F.A.C.P., Regent of the American College of Physicians, Madison, Wis., addressed the 95th session of the Iowa State Medical Society in Des Moines, Iowa.

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Dr. Allen W. Cowley, F.A.C.P., Harrisburg, Pa., was recently awarded the Seibert Memorial, given biennially by the Harrisburg Academy of Medicine. This award of \$500 is made to a physician under 45 who has "preëminently distinguished himself in his profession and whose life as a citizen and scholar has been broad, unselfish and exemplary."

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Dr. Reginald Fitz, F.A.C.P., Regent of the American College of Physicians, and Dr. Dwight O'Hara, F.A.C.P., both of Boston, Mass., spoke before the 50th anniversary dinner of the Tufts Medical Alumni Association on April 10.

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Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, delivered the fifth Edwin R. Kretschmer Memorial Lecture in Chicago on April 26.

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Dr. Stockton Kimball, F.A.C.P., Buffalo, N. Y., has been appointed Acting Dean of the University of Buffalo School of Medicine.

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Dr. Jean A. Curran, F.A.C.P., Brooklyn, N. Y., was a guest at the annual dinner given by the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn on February 20 in honor of sixteen ex-presidents of this society.

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The American Physicians Literary Guild was organized in San Francisco January 2, 1946. All physicians in America who write as an avocation are invited to join the guild. Nonmedical essays, monographs, short stories, or poems will be given competitive consideration by the guild for presentation at a literary exhibition during the annual session of the American Medical Association. Additional information may be obtained through Dr. F. H. Redewill, Secretary, Flood Building, San Francisco 2, Calif.

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Dr. Joseph Hughes (Associate), Philadelphia, has been appointed Professor of Psychiatry of the Woman's Medical College of Pennsylvania. At present he holds the rank of commander and is chief of the neuropsychiatric service at the Philadelphia Naval Hospital.

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Dr. Albert W. Lapin of Montreal, Canada, has been awarded a Clinical Fellowship in Medicine by the Committee on Fellowships and Awards of the American College of Physicians, beginning May 1, 1946.

Dr. Lapin plans to spend this clinical year at the University Hospital, Ann Arbor, Michigan, doing postgraduate work in Cardiology under Dr. Frank N. Wilson; also at the Massachusetts General Hospital under Dr. Paul D. White, and at Emory University under Dr. E. A. Stead.

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#### WESTERN MICHIGAN MEMBERS ORGANIZE FOR REGIONAL MEETINGS

On March 20, 1946, thirty-six Fellows met at Muskegon, Michigan, to organize a regional group, or chapter, of the American College of Physicians "to promote friendship and understanding among the Fellows and Associates in Western Michigan, and to foster scientific investigation in the field of internal medicine." "The College of Physicians of Western Michigan" was chosen as the name of the group, and membership shall be limited to Fellows and Associates of the American College of Physicians living in or adjacent to that area commonly called Western Michigan. The permanent management of the organization shall be vested in a Secretary who shall be elected at the first meeting of each calendar year by popular vote of those members present. Meetings shall be held three times a year, in the fall, winter and spring seasons, and the Secretary is charged with the responsibility of appointing a chairman of each meeting. The chairman shall arrange a suitable scientific program and make such other arrangements as necessary. The cost of conducting the meetings will be prorated among those in attendance.

Dr. Douglas Donald, Detroit, College Governor for Michigan, was in attendance and addressed the group. Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, acted as Chairman and Dr. William LeFevre, F.A.C.P., Muskegon, was appointed Secretary pro tempore, and was later formally elected Secretary.

Colonel A. R. Gaines, F.A.C.P., of the Percy Jones Hospital, addressed the dinner meeting at the Muskegon Country Club and presented an invitation for the next meeting to be held at the Percy Jones General Hospital, which invitation was accepted.

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#### BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

The Board of Trustees of Wake Forest College, at a meeting held in Wake Forest on March 26, acted favorably on an offer from the Z. Smith Reynolds Foundation of an endowment fund with a present market value of \$10,500,000. The charter of the Foundation provides that 20 per cent of the income be added to the principal until, through this and other contributions, it reaches \$50,000,000. The offer stipulated that Wake Forest College be moved to Winston-Salem, where the Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital are now located. Final decision in the matter will be made by the North Carolina Baptist State Convention. Officers and directors of the Z. Smith Reynolds Foundation are: W. N. Reynolds, President; Stratton Coyner, Secretary; Richard J. Reynolds, Mary Reynolds Babcock, Nancy Reynolds Bagley, and W. R. Hubner.

A gift of \$125,000 has been recently received from Gordon Gray, son of the late Bowman Gray. The greater portion of the gift will be used to develop a department of Psychiatry.

Dr. Lloyd J. Thompson, formerly a member of the staff of the department of Psychiatry of Yale University School of Medicine, and Chief Consultant in Psychiatry for the European Theatre during the war, has been elected Professor of Psychiatry and director of the department of Neuropsychiatry.

Drs. J. P. Davis, Charles H. Reid, Jr., and Joseph B. Stevens have been appointed to the faculty with the title of Assistant in Medicine.



The fourth Commencement of the Bowman Gray School of Medicine was held on March 24. Forty-two graduates were awarded the degree of Doctor of Medicine. Dr. Thomas T. Mackie of New York delivered the commencement address.

Dr. Wingate M. Johnson of the Department of Medicine spoke at the Annual Clinical Conference of the Chicago Medical Society on March 5. His subject was "The Management of the Patient with Peptic Ulcer."

Dr. George T. Harrell, Jr., of the Department of Medicine, took part in the program of the New Orleans Post-Graduate Medical Assembly, which was held April 1-4.

Dr. Robert P. Morehead of the Department of Pathology has been appointed educational director for the North Carolina division of the Field Army of the American Cancer Society.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to April 12, 1946 inclusive).

Sidney Adler, Detroit, Mich. (Comdr., MC, USNR)  
 Ralph I. Alford, Montclair, N. J. (Major, MC, AUS)  
 William H. Algie, Kansas City, Kan. (Comdr., MC, USNR)

John S. Bagwell, Dallas, Tex. (Major, MC, AUS)  
 Benjamin M. Baker, Jr., Baltimore, Md. (Colonel, MC, AUS)  
 Fred E. Ball, Chicago, Ill. (Lt. Col., MC, AUS)  
 Joseph Bank, Phoenix, Ariz. (Lt. Col., MC, AUS)  
 Lewis Barbato, San Antonio, Tex. (Major, MC, AUS)  
 Clarke H. Barnacle, Denver, Colo. (Lt. Col., MC, AUS)  
 Raymond L. Barrett, Springfield, Mass. (Lt. Col., MC, AUS)  
 Theodore B. Bayles, Boston, Mass. (Lt. Col., MC, AUS)  
 Morris B. Bender, New York, N. Y. (Comdr., MC, USNR)  
 Julien E. Benjamin, Cincinnati, Ohio (Colonel, MC, AUS)  
 Dudley W. Bennett, San Francisco, Calif. (Capt., MC, USNR)  
 James B. Berardi, Chicago, Ill. (Lt. Col., MC, AUS)  
 William G. Bernhard, Newark, N. J. (Lt. Col., MC, AUS)  
 Arthur Bernstein, Chicago, Ill. (Lt., MC, USNR)  
 Edward G. Billings, Denver, Colo. (Colonel, MC, AUS)  
 Charles T. Bingham, West Hartford, Conn. (Comdr., MC, USNR)  
 Benjamin J. Birk, Milwaukee, Wis. (Colonel, MC, AUS)  
 Belford C. Blaine, Pottsville, Pa. (Major, MC, AUS)  
 Theodore L. Bliss, Akron, Ohio (Colonel, MC, AUS)  
 Meyer Bloom, Johnstown, Pa. (Capt., MC, AUS)  
 Henry A. Bradford, Detroit, Mich. (Capt., MC, AUS)  
 James A. Bradley, St. Petersburg, Fla. (Lt. Comdr., MC, USNR)  
 Lewis W. Brown, Newark, N. J. (Comdr., MC, USNR)  
 Philip W. Brown, Rochester, Minn. (Lt. Col., MC, AUS)  
 Harvey C. Brownley, Lynchburg, Va. (Lt. Col., MC, AUS)  
 James G. Bruce, Springfield, Mass. (Major, MC, AUS)  
 Howard G. Bruenn, New York, N. Y. (Comdr., MC, USNR)  
 L. Clair Burket, Altoona, Pa. (Major, MC, AUS)

Walter S. Burrage, Boston, Mass. (Capt., MC, USNR)  
Hildahl I. Burtness, Santa Barbara, Calif. (Comdr., MC, USNR)  
W. Turner Bynum, Chickasha, Okla. (Lt., MC, USNR)

Richard B. Capps, Chicago, Ill. (Lt. Col., MC, AUS)  
Charles M. Caravati, Richmond, Va. (Colonel, MC, AUS)  
Louis H. Charney, Oklahoma City, Okla. (Lt. Col., MC, AUS)  
Eric MacMillan Chew, Seattle, Wash. (Lt. Col., MC, AUS)  
Austin B. Chinn, Washington, D. C. (Lt. Col., MC, AUS)  
Richard J. Clark, Winchester, Mass. (Major, MC, AUS)  
Thomas A. Clawson, Jr., Salt Lake City, Utah (Colonel, MC, AUS)  
Charles B. Coggin, Los Angeles, Calif. (Major, MC, AUS)  
Ben H. Cooley, Norman, Okla. (Colonel, MC, AUS)  
James E. Cottrell, Philadelphia, Pa. (Lt. Col., MC, AUS)  
H. Dick Countryman, Rockford, Ill. (Lt. Col., MC, AUS)  
George B. Craddock, Lynchburg, Va. (Major, MC, AUS)  
Robert M. Craig, Dayton, Ohio (P. A. Surgeon, USPHS(R))  
George W. Cramp, Brooklyn, N. Y. (Capt., MC, USNR)  
Joseph D. Croft, Evanston, Ill. (Comdr., MC, USNR)  
John K. Curtis, New York, N. Y. (Comdr., MC, USNR)  
Edward H. Cushing, Cleveland, Ohio (Capt., MC, USNR)

Charles M. Darnall, Austin, Tex. (Major, MC, AUS)  
Robert G. Davis, Washington, D. C. (Capt., MC, USN)  
Albert M. DeArmond, Indianapolis, Ind. (Lt. Col., MC, AUS)  
John K. Deegan, Ithaca, N. Y. (Major, MC, AUS)  
Edward A. Delarue, Jr., Richmond, Va. (Major, MC, AUS)  
William F. Dobyns, Aspinwall, Pa. (Lt. Col., MC, AUS)  
William M. Donohue, Houston, Tex. (Major, MC, AUS)  
Frederic G. Dorwart, Muskogee, Okla. (Lt. Col., MC, AUS)  
Albert H. Douglas, Jamaica, N. Y. (Comdr., MC, USNR)  
Alexander S. Dowling, Corning, N. Y. (Comdr., MC, USNR)  
Morris L. Drazin, Jackson Heights, L. I., N. Y. (Lt. Col., MC, AUS)  
Thomas J. Dry, Rochester, Minn. (Lt. Col., MC, AUS)  
Alfred W. Dubbs, Allentown, Pa. (Major, MC, AUS)  
Joseph L. Duffy, London, Ont., Can. (Lt. Col., RCAMC)  
Lawrence N. Durgin, Amherst, Mass. (Major, MC, AUS)  
Robert B. Durham, Atlantic City, N. J. (Comdr., MC, USNR)

Joseph C. Edwards, St. Louis, Mo. (Lt. Col., MC, AUS)  
Joseph C. Ehrlich, Chicago, Ill. (Lt. Col., MC, AUS)  
Herbert Eichert, Miami, Fla. (Lt. Comdr., MC, USNR)  
Clarence K. Elliott, Lincoln, Nebr. (Comdr., MC, USNR)  
F. George Elliott, Edmonton, Alta., Can. (Major, RCAMC)  
Ephraim P. Engleman, Boston, Mass. (Major, MC, AUS)  
Herbert K. Ensworth, New York, N. Y. (Major, MC, AUS)  
Clarence W. Erickson, Pittsburg, Kan. (Capt., MC, AUS)  
Richard D. Evans, Beverly Hills, Calif. (Lt. Col., MC, AUS)  
David W. Exley, Miami Beach, Fla. (Major, MC, AUS)

Elliston Farrell, New Orleans, La. (Lt. Col., MC, AUS)  
Marcus A. Feinstein, New York, N. Y. (Major, MC, AUS)  
James O. Finney, Gadsden, Ala. (Major, MC, AUS)  
Russell A. Flack, La Fayette, Ind. (Comdr., MC, USNR)  
Gerald Flaum, New York, N. Y. (Comdr., MC, USNR)  
Charles A. Flood, New York, N. Y. (Lt. Col., MC, AUS)  
Maurice P. Foley, Los Angeles, Calif. (Major, MC, AUS)  
John V. Fopeano, Kalamazoo, Mich. (Lt. Col., MC, AUS)  
Donald E. Forster, Portland, Ore. (Major, MC, AUS)  
Frank P. Foster, Boston, Mass. (Lt. Col., MC, AUS)

Leon J. Galinsky, Oakdale, Iowa (Major, MC, AUS)  
Clarence L. Gardner, Jr., Aurora, Ill. (Lt. Col., MC, AUS)  
Lawrence E. Geeslin, Atlanta, Ga. (Lt. Col., MC, AUS)  
Mark L. Gerstle, Jr., San Francisco, Calif. (Capt., MC, USNR)  
William T. Gibb, Jr., New York, N. Y. (Comdr., MC, USNR)  
Warren M. Gilbert, Rome, Ga. (Lt. Col., MC, AUS)  
Samuel M. Gingold, Detroit, Mich. (Major, MC, AUS)  
Harold I. Ginsberg, Detroit, Mich. (Capt., MC, AUS)  
Daniel A. Glomset, Rochester, Minn. (Capt., MC, AUS)  
Jacob S. Golden, Chicago, Ill. (Capt., MC, AUS)  
Walter Goldfarb, New York, N. Y. (Lt. Col., MC, AUS)  
Bernard A. Goldman, New Orleans, La. (Major, MC, AUS)  
Milton J. Goldstein, Scranton, Pa. (Major, MC, AUS)  
Robert W. Gordon, Denver, Colo. (Major, MC, AUS)  
G. Philip Grabfield, Boston, Mass. (Colonel, MC, AUS)  
Robert W. Graham, Ottawa, Ont., Can. (Major, RCAMC)  
Edward A. Greco, Portland, Maine (Lt. Col., MC, AUS)  
Emil H. Grieco, Bayonne, N. J. (Major, MC, AUS)  
William H. Griffith, Los Angeles, Calif. (Major, MC, AUS)  
Harold J. Gunderson, Everett, Wash. (Major, MC, AUS)  
Lewis Gunther, Los Angeles, Calif. (Comdr., MC, USNR)  
Ramsdell Gurney, Buffalo, N. Y. (Major, MC, AUS)

William E. Hall, Meriden, Conn. (Comdr., MC, USNR)  
George C. Ham, Charlottesville, Va. (Capt., MC, AUS)  
George C. Hamilton, Binghamton, N. Y. (Lt. Col., MC, AUS)  
Ian B. Hamilton, Canton, Ohio (Lt. Col., MC, AUS)  
Carl F. Hammerstrom, Jamestown, N. Y. (Lt. Col., MC, AUS)  
H. Phillip Hampton, Tampa, Fla. (Lt. Col., MC, AUS)  
J. Fletcher Hanson, Macon, Ga. (Lt. Col., MC, AUS)  
Benedict R. Harris, New Haven, Conn. (Comdr., MC, USNR)  
Robert P. Harvey, Limon, Colo. (Lt. Col., MC, AUS)  
Frederick K. Herpel, West Palm Beach, Fla. (Lt. Col., MC, AUS)  
Ford K. Hick, Chicago, Ill. (Colonel, MC, AUS)  
Charles S. Higley, Cleveland, Ohio (Lt. Col., MC, AUS)  
Donald A. Hirsch, Chicago, Ill. (Major, MC, AUS)  
Joseph H. Hodas, New York, N. Y. (Comdr., MC, USNR)  
Carl C. Hoffman, II, Harrisburg, Pa. (Major, MC, AUS)

Arthur A. Holbrook, Milwaukee, Wis. (Lt. Col., MC, AUS)  
W. Paul Holbrook, Tucson, Ariz. (Colonel, MC, AUS)  
Joseph L. Hollander, Philadelphia, Pa. (Major, MC, AUS)  
Thomas N. Horan, Detroit, Mich. (Major, MC, AUS)  
Benjamin Horn, Bridgeport, Conn. (Major, MC, AUS)  
Allen E. Hussar, New York, N. Y. (Lt. Col., MC, AUS)  
Adolph M. Hutter, Fond du Lac, Wis. (Comdr., MC, USNR)

Donald W. Ingham, Washington, D. C. (Lt. Col., MC, AUS)

Louis Jaffe, Detroit, Mich. (Capt., MC, AUS)  
Thomas C. Jaleski, New Rochelle, N. Y. (Comdr., MC, USNR)  
Edward R. Janjigian, Danville, Pa. (Major, MC, AUS)  
Benjamin Jeffries, Detroit, Mich. (S. A. Surgeon, USPHS(R))  
William N. Jenkins, Port Gibson, Miss. (Lt. Col., MC, AUS)  
Joseph F. Jenovese, Hartford, Conn. (Lt. Comdr., MC, USNR)  
Charles A. Jones, Philadelphia, Pa. (Lt. Comdr., MC, USNR)  
Robert H. Jordan, New Haven, Conn. (Major, MC, AUS)  
Allen I. Josey, Columbia, S. C. (Colonel, MC, AUS)  
Irving R. Juster, Glen Falls, N. Y. (Lt. Col., MC, AUS)

John S. Kapernick, Rochester, Minn. (Major, MC, AUS)  
George J. Kastlin, Pittsburgh, Pa. (Colonel, MC, AUS)  
H. Worley Kendell, Chicago, Ill. (Surgeon, USPHS(R))  
Baldwin L. Keyes, Philadelphia, Pa. (Colonel, MC, AUS)  
Ernest Q. King, Washington, D. C. (Lt. Col., MC, AUS)  
Otis G. King, Bluefield, W. Va. (Major, MC, AUS)  
J. Murray Kinsman, Louisville, Ky. (Lt. Col., MC, AUS)  
Elmer A. Kleefield, Forest Hills, N. Y. (Major, MC, AUS)  
Albert P. Knight, Waverly, N. Y. (Lt. Col., MC, AUS)  
George M. Knowles, Hackensack, N. J. (Lt. Col., MC, AUS)  
Samuel I. Kooperstein, Jersey City, N. J. (Lt. Col., MC, AUS)

Charles A. Landshof, Jersey City, N. J. (Lt. Col., MC, AUS)  
Harry E. Landt, Cincinnati, Ohio (Capt., MC, AUS)  
Louis B. Laplace, Philadelphia, Pa. (Colonel, MC, AUS)  
William H. Leake, Los Angeles, Calif. (Capt., MC, USNR)  
William V. Leary, Rochester, Minn. (Lt. Col., MC, AUS)  
Edward P. Leeper, Dallas, Tex. (Lt. Col., MC, AUS)  
Charles E. Lemmon, Detroit, Mich. (Lt. Col., MC, AUS)  
John B. Levan, Reading, Pa. (Lt. Col., MC, AUS)  
Robert C. Levy, Chicago, Ill. (Capt., MC, AUS)  
Howard P. Lewis, Portland, Ore. (Colonel, MC, AUS)  
Leon Lewis, New York, N. Y. (Comdr., MC, USNR)  
Harry R. Lipton, Atlanta, Ga. (Surgeon, USPHS(R))  
Joe H. Little, Mobile, Ala. (Lt. Col., MC, AUS)  
Leo W. Lloyd, Durango, Colo. (Capt., MC, AUS)  
Putnam C. Lloyd, New York, N. Y. (Lt. Col., MC, AUS)  
Robert B. Logue, Atlanta, Ga. (Lt. Col., MC, AUS)

Julian S. Long, Wilkes-Barre, Pa. (Major, MC, AUS)  
C. Ray Lounsberry, San Diego, Calif. (Capt., MC, USNR)  
William S. Love, Jr., Baltimore, Md. (Colonel, MC, AUS)  
Eugene L. Lozner, Boston, Mass. (Comdr., MC, USNR)  
Clayton J. Lundy, Chicago, Ill. (Major, MC, AUS)  
Ralph Lynch, Pittsburgh, Pa. (Lt. Col., MC, AUS)

Willard Machle, Cincinnati, Ohio (Colonel, MC, AUS)  
Thomas T. Mackie, New York, N. Y. (Colonel, MC, AUS)  
James M. MacMillan, Detroit, Mich. (Capt., MC, AUS)  
John E. Manley, Scranton, Pa. (Lt. Col., MC, AUS)  
Gilbert H. Marquardt, Chicago, Ill. (Colonel, MC, AUS)  
Douglas D. Martin, Tampa, Fla. (Comdr., MC, USNR)  
John W. Martin, Jr., Cleveland, Ohio (Lt. Comdr., MC, USNR)  
Thomas W. Martin, Pittsburgh, Pa. (Lt. Col., MC, AUS)  
Walter P. Martin, Santa Barbara, Calif. (Capt., MC, AUS)  
Arthur M. Master, New York, N. Y. (Capt., MC, USNR)  
J. Fred Mathers, Orlando, Fla. (Major, MC, AUS)  
Marsh McCall, New York, N. Y. (Lt. Col., MC, AUS)  
Arthur C. McCarty, Louisville, Ky. (Colonel, MC, AUS)  
David W. McCarty, Jr., Longmont, Colo. (Major, MC, AUS)  
Thomas C. McCleave, Jr., Oakland, Calif. (Comdr., MC, USNR)  
William O. McDonald, St. John, N. B., Can. (Lt. Col., RCAMC)  
James W. McElroy, Memphis, Tenn. (Capt., MC, AUS)  
Francis J. McEvoy, Royal Oak, Mich. (Comdr., MC, USNR)  
Sylvester McGinn, Boston, Mass. (Comdr., MC, USNR)  
A. Park McGinty, Atlanta, Ga. (Comdr., MC, USNR)  
G. Thomas McKean, Detroit, Mich. (Capt., MC, AUS)  
James B. McLester, Birmingham, Ala. (Colonel, MC, AUS)  
Ralph E. McLochlin, Little Rock, Ark. (Comdr., MC, USNR)  
Delbert H. McNamara, Santa Barbara, Calif. (Lt. Comdr., MC, USNR)  
Ronald J. McNamara, Charleston, W. Va. (Comdr., MC, USNR)  
James H. McNeill, North Wilkesboro, N. C. (Lt. Comdr., MC, USNR)  
Samuel Melamed, New York, N. Y. (Lt. Col., MC, AUS)  
Oliver J. Menard, Springfield, Mass. (Lt. Col., MC, AUS)  
Harold R. Merwarth, Brooklyn, N. Y. (Capt., MC, USNR)  
J. Roscoe Miller, Chicago, Ill. (Comdr., MC, USNR)  
Lawrence T. Minish, Jr., Louisville, Ky. (Lt. Col., MC, AUS)  
Robert H. Mitchell, Plainview, Tex. (Major, MC, AUS)  
Matthew Molitch, Atlantic City, N. J. (Lt. Col., MC, AUS)  
Henry A. Monat, Washington, D. C. (Capt., MC, USNR)  
Frank T. Moore, Akron, Ohio (Col., MC, AUS)  
Philip W. Morgan, Emporia, Kan. (Major, MC, AUS)  
Samuel Morrison, Baltimore, Md. (Lt. Col., MC, AUS)  
Alvin E. Murphy, Staten Island, N. Y. (Comdr., MC, USNR)  
Norman L. Murray, Summit, N. J. (Lt. Col., MC, AUS)

Marshall G. Nims, Denver, Colo. (Major, MC, AUS)  
F. Garm Norbury, Jacksonville, Ill. (Col., MC, AUS)

Leo L. Orenstein, New York, N. Y. (Major, MC, AUS)  
 Bergein M. Overholt, Knoxville, Tenn. (Lt. Col., MC, AUS)  
 George C. Owen, Oshkosh, Wis. (Lt. Col., MC, AUS)

Christopher Parnall, Jr., Rochester, N. Y. (Lt. Col., MC, AUS)  
 John W. Parsons, Baltimore, Md. (Comdr., MC, USNR)  
 Ross Paull, La Jolla, Calif. (Colonel, MC, AUS)  
 Julius R. Pearson, Miami Beach, Fla. (Major, MC, AUS)  
 L. Lewis Pennock, Pittsburgh, Pa. (Major, MC, AUS)  
 Evans W. Pernokis, Chicago, Ill. (Comdr., MC, USNR)  
 Cornelius C. Perrine, Fair Haven, N. J. (Lt. Comdr., MC, USNR)  
 Carey M. Peters, Boston, Mass. (Major, MC, AUS)  
 Michael Peters, Telford, Pa. (Major, MC, AUS)  
 Frank P. Pignataro, Marlboro, N. J. (Lt. Col., MC, AUS)  
 Harry H. Pote, Philadelphia, Pa. (Lt. Comdr., MC, USNR)  
 Frederick C. Potter, Cuyahoga Falls, Ohio (Lt. Col., MC, AUS)  
 Alvin E. Price, Detroit, Mich. (Lt. Col., MC, AUS)

Frank B. Queen, Chicago, Ill. (Colonel, MC, AUS)  
 Kenneth E. Quickel, Harrisburg, Pa. (Lt., MC, USNR)  
 Warren W. Quillian, Coral Gables, Fla. (Comdr., MC, USNR)

Herbert W. Rathe, Waverly, Iowa (Lt. Col., MC, AUS)  
 Edward P. Reh, St. Louis, Mo. (Major, MC, AUS)  
 John A. Reisinger, Chevy Chase, Md. (Capt., MC, USNR)  
 H. Walden Retan, Syracuse, N. Y. (Comdr., MC, USNR)  
 William F. Rexer, Brooklyn, N. Y. (Major, MC, AUS)  
 John M. Rice, Watertown, N. Y. (Major, MC, AUS)  
 Murray L. Rich, Covington, Ky. (Lt. Col., MC, AUS)  
 Alexander D. Robertson, Willard, Ohio (Major, MC, AUS)  
 Harold A. Robinson, Detroit, Mich. (Major, MC, AUS)  
 Edwin J. Rose, Washington, D. C. (Colonel, MC, AUS)  
 Louis Rosenbaum, New York, N. Y. (Capt., MC, AUS)  
 Andrew I. Rosenberger, Milwaukee, Wis. (Major, MC, AUS)  
 Theodore B. Russell, New York, N. Y. (Comdr., MC, USNR)  
 Benjamin H. Rutledge, Baltimore, Md. (Colonel, MC, AUS)  
 David I. Rutledge, Boston, Mass. (Major, MC, AUS)  
 Edward J. Ryan, Cleveland, Ohio (Lt. Comdr., MC, USNR)

Albert C. Santy, New York, N. Y. (Comdr., MC, USNR)  
 Milton S. Saslaw, Miami, Fla. (Major, MC, AUS)  
 Newton T. Saxl, New York, N. Y. (Capt., MC, USNR)  
 Robert L. Schaefer, Detroit, Mich. (Lt. Comdr., MC, USNR)  
 Edward W. Schoenheit, Asheville, N. C. (Comdr., MC, USNR)  
 Bernard M. Scholder, Mt. Vernon, N. Y. (Comdr., MC, USNR)  
 Arthur F. Schultz, Ft. Thomas, Ky. (Major, MC, AUS)  
 Robert Schwartz, Aspinwall, Pa. (Lt. Col., MC, AUS)  
 George X. Schwemlein, Cincinnati, Ohio (Capt., USPHS(R))  
 Edward V. Sexton, Teaneck, N. J. (Lt. Comdr., MC, USNR)

Edward G. Seybold, Jackson, Mich. (Capt., MC, AUS)  
Louis B. Shapiro, Manteno, Ill. (Lt. Col., MC, AUS)  
Samuel A. Shelburne, Dallas, Tex. (Capt., MC, USNR)  
John McFarland Sheldon, Ann Arbor, Mich. (Colonel, MC, AUS)  
Karl Shepard, High Point, N. C. (Capt., MC, AUS)  
Kenneth K. Sherwood, Seattle, Wash. (Major, MC, AUS)  
Leonard B. Shpiner, Boston, Mass. (Major, MC, AUS)  
Walter M. Simpson, Dayton, Ohio (Capt., MC, USNR)  
Elmer R. Smith, Ancon, C. Z. (Lt. Col., MC, AUS)  
Lucian A. Smith, Rochester, Minn. (Major, MC, AUS)  
Wilson F. Smith, Hartford, Conn. (Lt. Col., MC, AUS)  
Albert M. Snell, Rochester, Minn. (Capt., MC, USNR)  
Edward D. Spalding, Grosse Pointe Farms, Mich. (Lt. Col., MC, AUS)  
Russell J. Spivey, Indianapolis, Ind. (Major, MC, AUS)  
Aaron A. Sprong, Sterling, Kan. (Major, MC, AUS)  
John S. Staneslow, Waterbury, Conn. (Lt. Comdr., MC, USNR)  
Richard P. Stetson, Boston, Mass. (Lt. Col., MC, AUS)  
Russell A. Stevens, Wilkes-Barre, Pa. (Lt. Comdr., MC, USNR)  
Gilbert M. Stevenson, Ancon, C. Z. (Major, MC, AUS)  
Sloan G. Stewart, Atlantic City, N. J. (Colonel, MC, AUS)  
Andrew B. Stockton, San Francisco, Calif. (Comdr., MC, USNR)  
Charles F. Stone, Jr., Atlanta, Ga. (Capt., MC, AUS)  
William E. Storey, Columbus, Ga. (Major, MC, AUS)  
Cyrus W. Strickler, Jr., Atlanta, Ga. (Major, MC, AUS)  
William J. Sullivan, Bronxville, N. Y. (Lt. Comdr., MC, USNR)  
Horatio B. Sweetser, Jr., Minneapolis, Minn. (Capt., MC, USNR)  
Ralph E. Swope, New York, N. Y. (Major, MC, AUS)

Henry M. Tabachnick, Portland, Maine (Major, MC, AUS)  
R. Henry Temple, Kinston, N. C. (Major, MC, AUS)  
Lyndon H. Thatcher, Poughkeepsie, N. Y. (Major, MC, AUS)  
Charles M. Thompson, Philadelphia, Pa. (Comdr., MC, USNR)  
Jan H. Tillisch, Rochester, Minn. (Major, MC, AUS)  
Elam C. Toone, Jr., Richmond, Va. (Lt. Col., MC, AUS)  
James H. Townsend, Boston, Mass. (Lt. Col., MC, AUS)  
John W. Trenis, Washington, D. C. (Major, MC, AUS)  
William H. Trimble, Atlanta, Ga. (Lt. Col., MC, AUS)  
Arthur M. Tunick, New York, N. Y. (Lt. Col., MC, AUS)  
Arthur R. Twiss, Oakland, Calif. (Major, MC, AUS)

Harold L. Vyner, Brentwood, N. Y. (Major, MC, AUS)

Don C. Wakeman, Topeka, Kan. (Lt. Col., MC, AUS)  
Joe Edmund Walker, Long Beach, Calif. (Capt., MC, USNR)  
Emmett D. Wall, Chicago, Ill. (Lt. Col., MC, AUS)  
Albert W. Wallace, Miami Beach, Fla. (Colonel, MC, AUS)  
C. Stewart Wallace, Ithaca, N. Y. (Comdr., MC, USNR)  
E. Richmond Ware, Los Angeles, Calif. (Lt. Col., MC, AUS)  
Leon H. Warren, Philadelphia, Pa. (Lt. Col., MC, AUS)

Harry Warshawsky, West Lebanon, N. H. (Lt. Col., MC, AUS)  
 Richard N. Washburn, Rensselaer, Ind. (Lt. Col., MC, AUS)  
 Sydney P. Waud, Chicago, Ill. (Lt. Col., MC, AUS)  
 Solomon C. Werch, Chicago, Ill. (Capt., MC, AUS)  
 George K. Wever, Stockton, Calif. (Major, MC, AUS)  
 R. James Wharton, Johnson City, N. Y. (Colonel, MC, AUS)  
 John C. White, New Britain, Conn. (Comdr., MC, USNR)  
 Benjamin V. White, Hartford, Conn. (Lt., MC, USNR)  
 Roger S. Whitney, Colorado Springs, Colo. (Major, MC, AUS)  
 Dwight L. Wilbur, San Francisco, Calif. (Comdr., MC, USNR)  
 John H. Willard, Philadelphia, Pa. (Comdr., MC, USNR)  
 Olin G. Wilson, Canton, Ohio (Major, MC, AUS)  
 William H. Windley, Washington, N. C. (Major, MC, AUS)  
 Alfred M. Wolfe, Denver, Colo. (Comdr., MC, USNR)  
 Bernard P. Wolff, Atlanta, Ga. (Lt. Col., MC, AUS)  
 Bertrand O. Woods, Portland, Ore. (Colonel, MC, AUS)  
 Robert M. Woods, Milwaukee, Wis. (Capt., MC, AUS)  
 Jackson W. Wright, Cincinnati, Ohio (Major, MC, AUS)

Asher Yaguda, Newark, N. J. (Comdr., MC, USNR)

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Selection of Dr. Ernest W. Goodpasture, Professor of Pathology and Dean of the School of Medicine of Vanderbilt University, Nashville, Tennessee, as the 1946 recipient of the Passano Foundation Award has been announced by the Board of Directors of the Foundation. Presentation of the \$5000 cash award will be made at an appropriate ceremony in historic Osler Hall of the Medical and Chirurgical Faculty of Maryland, in Baltimore, on the night of May 15.

The Foundation, which was established in 1944 by the Williams and Wilkins Company, Medical Publishers, of Baltimore, proposes to aid in any way possible the advancement of medical research, especially research that bears promise of clinical application. For the encouragement of such research the Foundation has established the award as one of its activities.

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School; Dr. Nicholson J. Eastman, Professor of Obstetrics in the Johns Hopkins University Medical School; Dr. George W. Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington, represent the medical profession on the Board of Directors of The Foundation.

Following the presentation of the award by Mr. Edward B. Passano, Chairman of the Board of The Williams & Wilkins Company, Dr. Goodpasture will deliver an address entitled, "Research and Medical Practice."

Dr. Goodpasture receives the award for his original development of the method for propagation of viruses in pure culture by inoculation of chick embryos and for his outstanding contributions to advancement of knowledge of the cell-parasite relationship in bacterial and virus infection.

Prior to Dr. Goodpasture's development of the chick embryo method of propagation of viruses in pure culture, medical research was halted in attempts to study diseases caused by viruses because of the fact that viruses will not multiply in culture media as do bacteria. Therefore virus cultures could not be made available for research into the mechanism of their reactions.



As a result of Dr. Goodpasture's original discovery some ten years ago our knowledge of virus diseases has been immeasurably advanced. New viruses have been identified, the mechanism of virus reactions in the host has been studied and means of protection against many virus diseases have been made possible. Vaccines against several diseases of both man and animal against which little if any protection existed before have now been developed. Defenses against such diseases as fowlpox, smallpox, yellow fever, influenza and typhus fever have been considerably advanced by chick embryo study methods.

*OBITUARIES*

## DR. RALPH CHARLES MATSON

Dr. Ralph Charles Matson, F.A.C.P., Portland, Oregon, passed away on October 26, 1945.

Born January 21, 1880, Dr. Matson received his medical degree from the University of Oregon School of Medicine in 1902. He had extensive post-graduate study at St. Mary's Hospital, London; University of Vienna; University of Berlin; Academy of Medicine, Düsseldorf, Germany; the Brauer Clinic of Hamburg, Germany; and the Victoria Park and Brompton Hospitals of London.

Dr. Matson was head of the Department of Bacteriology at his Alma Mater, later, Associate Clinical Professor of Medicine and Associate Clinical Professor of Surgery, where he had been a member of the Executive Faculty and Co-Director of the Tuberculosis Clinic. He served during World War I as Chief of the Medical Staff, General Hospital No. 21, now the Fitzsimons General Hospital, Denver; Chest Consultant, Multnomah County Hospital and Veterans Administration Facility at Portland. He was the Director of the Department of Thoracic Surgery, Portland Open Air Sanatorium; Visiting Physician, Good Samaritan Hospital and member of the Associate Medical Advisory Board of the National Jewish Hospital of Denver and honorary member of the Staff of the Lymanhurst School for Tuberculosis, Minneapolis; Chairman, Editorial Board, "Diseases of the Chest," and member of the Editorial Board, "Western Journal of Surgery, Obstetrics and Gynecology." He was also Chief Surgeon of the University State Tuberculosis Hospital.

Dr. Matson was also author of numerous articles in English, French and German, dealing with the diagnosis, medical and surgical treatment of pulmonary, tuberculosis, and contributor of sections of several books.

He was a member of the Portland Academy of Medicine, Pacific Interurban Clinical Club, Pacific Coast Surgical Association, American Association for Thoracic Surgery, Oregon State Tuberculosis Society, American Clinical and Climatological Association and American Trudeau Society. He was an honorary member of the Hollywood Academy of Medicine, Minneapolis Surgical Society, Kansas City Southwest Clinical Society and Eastern Oregon District Medical Society. In 1938, he was Vice-Chairman of Thoracic Section, Pan-Pacific Medical Association; Past President, American Sanatorium Association; Past President and member of the Board of Regents of the American College of Chest Physicians; former Vice-President and Director of the National Tuberculosis Association. He was a Fellow of the American College of Surgeons and International College of Surgeons; also a Fellow of the American College of Physicians since 1917.

## DR. GEORGE JESSE WRIGHT

Dr. George Jesse Wright, F.A.C.P., Pittsburgh, Pennsylvania, died October 1, 1945, in the Toronto General Hospital, Toronto, Ontario, Canada, at the age of 65, of nephritis.

Born in Pittsburgh, June 1, 1880, Dr. Wright received his A.B. Degree from Harvard University in 1900 and the degree of Doctor of Medicine from the University of Pennsylvania School of Medicine in 1904. His post-graduate appointments were served at the Pennsylvania Hospital in Philadelphia, the Neurological Institute in New York and the Boston Psychopathic Hospital. He was a diplomate of the American Board of Psychiatry and Neurology and member of the American Neurological Association, the American Psychiatric Association and the Association for Research in Nervous and Mental Diseases. For many years, Dr. Wright was Professor of Neurology at the University of Pittsburgh School of Medicine. He became a Fellow of the American College of Physicians in 1931.

Formerly President of the Pennsylvania Psychiatric Society, Dr. Wright was Neurologist to the St. Margaret's Memorial, Mercy, St. Francis and Allegheny General Hospitals in Pittsburgh. He also served as Visiting Neurologist at St. Joseph's Hospital and Dispensary.

His professional services will be sorely missed by his colleagues in western Pennsylvania. The American College of Physicians has lost an outstanding Fellow.

## DR. WILLIAM WADDLE RICHARDSON

Dr. William Waddle Richardson, F.A.C.P., died at the Mercer Sanitarium, Mercer, Pa., on June 10, 1945, at the age of 67, of cerebral hemorrhage.

Born in Athens, Ohio, October 8, 1877, Dr. Richardson received his Medical Degree from the University of Pennsylvania School of Medicine in 1902. He pursued postgraduate study in Neurology and Psychiatry at the Psychiatric Clinic, Munich, at the Harvard Medical School, and at the New York Neurological Institute. He received his basic intern training at the Philadelphia General Hospital, and served as Chief Physician to the Norristown (Pa.) State Hospital. For many years he was Medical Director of the Mercer Sanitarium, Mercer, Pa., and Consulting Neuropsychiatrist to the Christian H. Buhl Hospital in Sharon, Pa. He was a member of Beta Theta Pi, Phi Beta Kappa, and Sigma Xi.

Dr. Richardson was a diplomate of the American Board of Psychiatry and Neurology, and was twice elected President of the Mercer County Medical Society. He was a member of the Pennsylvania State Medical Society, the Pittsburgh Neurological Society, the Association for Research in Nervous and Mental Diseases, and also a member of the Central Neuropsychiatric Association.

During World War I, he served in France with the rank of Major in the Medical Corps as Neurologist with Base Hospital No. 11. During World War II, he was Chairman of the Medical Advisory Board No. 10 of the Pennsylvania Selective Service. He became a Fellow of the American College of Physicians in 1923.

#### DR. WILLIAM VIRGIL WATSON

William Virgil Watson, M.B., F.A.C.P., Toronto, Ontario, Canada, passed away on October 20, 1945.

Born October 31, 1886, Dr. Watson received his M.B. Degree from the University of Toronto Faculty of Medicine in 1914. He served his internship at the Toronto General Hospital, and for many years was a Demonstrator in Therapeutics at his Alma Mater. His private practice was limited to Internal Medicine and Metabolic Diseases. He was author of several published articles which reflected his grasp of Internal Medicine and Metabolism.

Dr. Watson was a member of the Toronto Academy of Medicine, the Ontario Medical Association, Canadian Medical Association and the American Association for the Advancement of Science. He became a Fellow of the American College of Physicians in 1931.

#### DR. THOMAS GOTTHART JENNY

Dr. Thomas Gotthart Jenny, Associate, died in Miami, Florida on August 31, 1945 at the age of 55, of coronary heart disease and nephritis.

Born September 12, 1885, Dr. Jenny received his medical degree from the University of Pittsburgh School of Medicine in 1907. He limited his practice to Internal Medicine and Cardiology, and was a member of the staff of Western Pennsylvania Hospital. He was also a member of the Allegheny County Medical Society and the Pennsylvania State Medical Association. He was a Fellow of the American Medical Association and had been an Associate of the American College of Physicians since 1924 by virtue of former membership in the American Congress on Internal Medicine.

His active professional life was spent in Pittsburgh, but he retired a year or two ago and moved to Miami, Florida.

#### DR. CLIFFORD DAVID MERCER

Clifford David Mercer, M.D., F.A.C.P., died December 25, 1945, after an illness of five years with coronary occlusion and complications. Dr. Mercer was born at Addison, Michigan, 1884; he attended the University of Michigan Medical School, 1904-1906; received his M.D. degree, 1908, from Northwestern University Medical School. He served as Resident Physician at the Uniontown Hospital (Pennsylvania), 1908-1909. For many

years he was a member of the staff of the West Union Community Hospital, Commissioner of Insanity, Fayette County, served as Internist on Medical Advisory Board No. 1, Iowa Selective Service, during World War II. He was former President of the Fayette County Medical Society, member of the Iowa State Medical Society, American Medical Association, Iowa Public Health Association; Fellow of the American College of Physicians since 1927 and recently a Life Member.

Dr. Mercer was a quiet, earnest conscientious physician, well loved in his community and respected by his medical colleagues throughout the State.

B. F. WOLVERTON, M.D., F.A.C.P.,  
Governor for Iowa

### DR. MAXIMILIAN A. RAMIREZ

Dr. Maximilian A. Ramirez, F.A.C.P., of New York City died on March 4, 1946. Dr. Ramirez was born in Cuba in 1890. He had been a Fellow of the College since 1924. He was educated in the University and Bellevue Medical School and since that time had been very closely connected with the New York Polyclinic Medical School and Hospital. At the time of his death he was Professor of Medicine and Attending Physician at the Polyclinic Medical School and Hospital. He also was Visiting Physician and Director of the Second Medical Division, French Hospital; was director of the Department of Immunology in the French Hospital; Visiting Physician City Hospital; Visiting Physician, Otisville Municipal Sanatorium; Consulting Physician St. Francis Hospital, Poughkeepsie; Consulting Physician, St. Agnes Hospital, White Plains; Consulting Physician, St. Clare's Hospital; Consulting Immunologist Broad Street Hospital.

He served as a first lieutenant in the Medical Corps of the Army in the first World War, was made a Chevalier of the Legion of Honor in 1933, and was presented with a plaque by the Honor Legion of the New York Police Department for his work as honorary consulting police surgeon.

He was a member of the New York Academy of Medicine, and Past President and Trustee of the Medical Society of the County of New York.

He was the author of numerous published papers, and his many friends will mourn the passing of a distinguished doctor.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. EDWIN LESLIE GARDNER

"The life of the dead consists in being present in the minds of the living."  
—Cicero.

Edwin Leslie Gardner, B.S., M.D., F.A.C.P., Minneapolis, Minnesota, died at his home, January 29, 1946, at the age of 59 years, following a two-year illness. Dr. Gardner, son of William C. and Eva Gardner, was born

August 2, 1886, in Jacksonville, Illinois. He received his high school education at Belmont Military Academy, Belmont, California; entered the University of Minnesota in 1906, and after two years in the College of Science, Literature and Arts, entered the Medical School and was graduated in 1912. He was a member of Nu Sigma Nu and Alpha Omega Alpha. He held first rank in a class of thirty, and was awarded the Bell prize in physical diagnosis. He served an internship at the Elliot Memorial Hospital and subsequently became assistant to Dr. J. W. Bell, after which he started his career in his chosen specialty, internal medicine.

His society memberships included: Hennepin County Medical Society, (President 1930); Minnesota State Medical Society, (Editing and Publishing Committee of Minnesota Medicine); American Medical Association; Minnesota Pathological Society (President); Minneapolis Clinical Club (President); Minnesota Academy of Medicine (Secretary); Minnesota Society of Internal Medicine (President); American College of Physicians. He was a member of the faculty of the University of Minnesota Medical School, and was attending physician at the Minneapolis General Hospital from 1914 to 1926.

At various times he was on the staff of Glen Lake Sanatorium, St. Mary's, Eitel, Asbury and Northwestern Hospitals. He was associated with Drs. L. S. Ylvisaker, Robert Kennecott, Paul Rowe, Lewis Daniels, Willard White, Charles A. Hallberg, R. S. Ylvisaker and the writer. He was a member of Hennepin Avenue Methodist Church, the University Club and the Professional Men's Club.

He was much the same, both as an undergraduate and as a practitioner, always serious minded and with a singleness of purpose—had he been born a few decades earlier he would have been known as a pioneer, possessing that industry and diligence characteristic of the self-made man. His secret of life was work. It was a habit so ingrained that it brought him the respect of his teachers and confreres, and a large clientele. When later he took up the avocations of photography and music he followed these in the same arduous way that he applied to medicine. In fact, it is more than likely that this not unmingled virtue contributed to his early demise.

T. A. PEPPARD, M.D.

#### DR. O. F. GOBER

On January 26, 1946, Dr. Olin Farris Gober, F.A.C.P., of Temple, Texas, died suddenly from a heart attack while on duty at Temple Hospital.

Dr. Gober was born in Jackson County, Georgia, on April 4, 1878, being educated in Texas, graduating from the University of Texas Medical Department in 1905. From 1918 he was Chief Physician of the Gulf, Colorado and Santa Fe Railroad, and was head of their Medical Service in Texas. Since 1926 Dr. Gober has been a Fellow of the American College of Physicians.

Spending his entire medical life in Temple, Texas, Dr. Gober was an active member of the staff of Scott and White Clinic, in addition to his large industrial practice. During his forty years of practice in Texas, he was an active worker in both medical and civic affairs, giving freely of his time and counsel when called upon. His kindly personality, understanding nature, and deep sincerity of purpose made him universally loved by everyone who knew him. He is survived by his son, Dr. Olin B. Gober, of Temple, Texas, his wife having died in 1944.

Dr. Gober's passing will be mourned by a host of friends throughout the Southwest, who will remember him always as an ideal physician who never spared himself when there was a service to be performed.

M. D. LEVY, F.A.C.P.,  
Governor for Texas

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## THE DOCTOR, THE PATIENT, AND THE TRUTH \*

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WHEN Pilate asked Jesus, "What is the truth?", He did not answer.<sup>1</sup> After a doctor has completed a careful examination he will frequently be in possession of information about a patient that will indicate to him quite definitely that the patient is suffering from a serious disease which is in a probably or possibly curable condition if a certain course of treatment or of surgery is carried out promptly. Should he then and there tell the patient "the truth, the whole truth, and nothing but the truth" and then ask the patient to let him arrange for the treatment? Is it *possible* to convey the "truth" about a serious matter to a patient? Henderson<sup>2</sup> has discussed this subject in an article that should be read by every one interested, and gives the following example:

"Consider the statement, 'This is a carcinoma.' . . . Let us assume . . . that the statement has nearly the same validity as the assertions in the nautical almanac. If we now look at things, not from the standpoint of philosophers, moralists or lawyers, but from the standpoint of biologists, we may regard the statement as a stimulus applied to the patient. This stimulus will produce a response and the response, together with the mechanism that is involved in its production is an extremely complex one, at least in those cases where a not too vague cognition of the meaning of the four words is involved in the process. . . . With the cognition there is a correlated fear. There will be a concern for the economic interests of others for example, of wife and children. I suggest, in view of these obvious facts that if you recognize the duty of telling the truth to the patient, you range yourself outside the class of biologists, with lawyers and philosophers. The idea that the truth, the whole truth, and nothing but the truth can be conveyed to the patient is an example of false abstraction, of that fallacy called by White-

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head,<sup>3</sup> 'The fallacy of misplaced concreteness.' It results from neglecting factors that cannot be excluded from the concrete situation and that have an effect that cannot be neglected. Another fallacy also is involved, the belief that it is not too difficult to know the truth; but of this I will not speak further.

"I beg that you will not suppose that I am recommending, for this reason, that you should always lie to your patients. Such a conclusion from what I have said would correspond roughly to a class of fallacies that I have already referred to above. Since telling the truth is impossible, there can be no sharp distinction between what is true and what is false. But surely that does not relieve the physician of his moral responsibility. On the contrary the difficulties that arise from the immense complexity of the phenomena do not diminish, but rather increase, the moral responsibility of the physician, and one of my objects has been to describe the facts through which the nature of that moral responsibility is determined.

"Far older than the precept, 'the truth, the whole truth, and nothing but the truth,' is another that originates within our profession, that has always been the guide of the best physicians, and, if I may venture a prophecy, will always remain so: So far as possible, 'Do no harm.' You can do harm by the process that is quaintly called telling the truth. You can do harm by lying. In your relations with your patients you will inevitably do much harm, and this will be by no means confined to your strictly medical blunders. It will also arise from what you say and what you fail to say. But try to do as little harm as possible, not only in treatment with drugs, or with the knife, but also in treatment with words, with the expression of your sentiments and emotions. Try at all times to act upon the patient so as to modify his sentiments to his own advantage, and remember that, to this end, nothing is more effective than arousing in him the belief that you are concerned wholeheartedly and exclusively for his welfare."

In any group of patients with identical surgical or medical conditions there will be a very wide variation in their mental states, physical states, social circumstances, and in the amount of information or misinformation concerning disease in their possession. Let us assume that a group of patients has gone to a man who is their final authority because they believe him to be an expert in the care of such cases. The doctor considers himself equipped by knowledge and training to assume this responsibility. All examinations have been completed and the doctor knows that the patients have carcinoma of the breast. If he operates on them there is essentially no danger of immediate death and after operation, according to known average results in cases at this particular stage of the disease, one half the group will survive five years without recurrence of the disease. But he does not know at this time and has no further tests to use to differentiate the potentially cured patients from the potential failures. Also let us assume that if operation is not done promptly but is done later, the chance of cure declines progressively. Also that treatment by other means, such as radiation, would

result in only one cure out of the group and again that there is no way to predict which case would receive this fortunate result. Also let us assume that all patients want very earnestly to live but that all of them would prefer to have any reasonable treatment short of surgery. It is clear that in these situations the most important accomplishment for the benefit of the patients is to secure their prompt consent to operations.

Now suppose a blunt doctor starts his conversations with the statement, "This is a cancer," and follows up by outlining all the facts in the assumptions given above. This statement will be given a very different interpretation by each of 10 different patients and none of them will interpret from it exactly what is going on in the doctor's mind. Many will interpret "cancer" as identical in meaning with "hopeless cancer." Perhaps eight of the patients might consent to proper operations but of these half might never forgive the doctor for his brutality. One of the remaining two might be among the number of people who believe erroneously that cancer is never cured and therefore decide to have no treatment. The other might be so upset mentally that she leaves the doctor and goes to a charlatan in whose hands all hope of cure will be lost.

On the other hand, suppose the doctor avoids the word cancer and minimizes the seriousness of the situation. Again eight patients consent. However, of these eight the one who recurred the earliest will blame the doctor by stating that the operation was not worth while and if she had known how serious the condition was she would not have consented. The other two refuse operation by telling the doctor they need time to make arrangements but in reality because they have not taken in the urgency of the situation, and as a result they delay so long they lose their chance of cure.

It is seen then that blunt "truth" is not good and that avoidance of truth may be as bad. How then should the doctor proceed with such an interview with some hope of doing no harm or at least of doing less harm to his patients?

Certainly at the start of the interview he should avoid the words carcinoma or cancer. He should use cyst, nodule, tumor, lesion, or some other loosely descriptive word that has not so many frightening connotations. He should then suggest that operation is indicated and give some rough idea of the extent of the operation. If consent is given at this stage, this is enough. But he should inform the most interested relative that there is only a 50 per cent chance of a successful outcome. Again, however, two patients in the group that are handled in this way are also resistive to the idea of operation. Now, however, no bridges have been crossed and many resources are still open to the doctor to secure consent for proper treatment. In one case the matter may be presented to the family and the family doctor who can take over at this point and who can frequently present the situation in such a light that the patient will consent. The other patient, however, is in a situation not infrequently encountered and has no family or family doctor who can be asked to assist. For instance, a patient who has warned

you in advance that she does not want her husband to be told anything because he is not well himself. In this situation, it seems clear that the doctor can only fully meet his obligations to the patient if she makes her final decision after being put in possession of as close approximation to the truth as can fairly be conveyed to her. One should, at least, state that the lesion is in imminent danger of becoming a cancer and that a good chance of cure still remains if action is immediate. If the patient asks directly, "Is this cancer?" the doctor is forced to answer, "Yes," but can always go on to explain in the same sentence, "but it probably is not as serious as you fear because you have a good chance of cure." In this way he can reduce greatly the shock that always is associated with the bald assertion.

After operation, the first things many patients want to know are what was found, what was done, and what is the expected result? What should the doctor tell the patient at this time? When the patient is still under the influence of opiates or sedatives, he must be told nothing because of great danger that the simplest statement will be misunderstood. Later, however, at a more opportune time, the doctor must be frank. In spite of the frequent requests by relatives not to do so, the patient should almost always be told exactly what was found at operation and exactly what was done. Harsh words and bald facts should be tempered to a reasonable degree. If the outlook is probably but not surely favorable, this statement must be made so that the patient will coöperate properly in follow up examinations or treatments necessary to prompt recognition and care of any sequelae. If the outlook is thoroughly bad and the doctor is quite sure the patient will die shortly what should he do? Of course, tell the responsible relative at once. His procedure with regard to the patient must vary with different patients. Usually the variations in procedure should be according to the patient's expressed desires. Almost always it does more good than harm to tell the patient who is in a hopeless situation the truth about his prospects. This must always be done gently, and perhaps, indirectly. A question as to whether the patient would like to see his clergyman or to make his will would mean much to some patients. Following such a suggestion the patient will often ask a direct question and should be given a direct answer. It was the author's duty as an intern to break the news to an old man from another state that the surgeons could do nothing further for his bladder carcinoma and that he might go home. While I was "beating around the bush" in a clumsy way, the man understood what was meant and said "You should not be afraid to tell me that I am going to die. I thought I was, but came down here to make sure. I will go home perfectly happy."

One reason it usually does good to patients to tell them their outlook is hopeless is that dying patients usually have a fairly good insight into their condition and the shock of confirming this belief is not great. Another reason is that they can relax and stop struggling to do all the things they have previously been doing to try to get well and to keep up their own or their family's morale. On the other hand, there are unusual patients suf-

fering from fatal illnesses who ask the doctor not to tell them anything. Such a request is in quite a different category from a request of the relatives. Usually it means that they have decided themselves that the situation is hopeless but they cannot bear to be told about it. If this is true, and if the patient is allowing all measures important to her comfort to be carried out, everything is to be gained by acceding to her request. Such a patient frequently shows great courage in facing the unpleasant facts of her disease during the process of dying.

#### SUMMARY

The doctor is bound in his duty to his patient to do whatever is best for his patient and to avoid doing him harm.

In discussing his patient's condition, the doctor realizes that there are some circumstances when he cannot, for the patient's own good, tell him the "whole truth."

However, there are other frequent circumstances in which friends and relatives want the "whole truth" (unpleasant) kept from the patient when it is much better for the patient for the doctor to be quite frank.

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# LEGAL PRIVILEGE, ON THERAPEUTIC GROUNDS, TO WITHHOLD SPECIFIC DIAGNOSIS FROM PATIENT SICK WITH SERIOUS OR FATAL ILLNESS \*

By HUBERT WINSTON SMITH,† LL.B., M.D., *Urbana, Illinois*

WHEN one says the first word on a controversial subject, he should not delude himself into thinking that he will have an opportunity to say the last. Sometimes, however, it is discreet to amplify what one said in the beginning, before others may bring the subject to a more mature and annihilating conclusion. In 1942, in the course of discussing select legal problems which arise in the practice of surgery,<sup>1</sup> the writer ventured the statement: "There is probably a privilege, on therapeutic grounds, to withhold the specific diagnosis where the disclosure of cancer or some other dread condition would seriously jeopardize the recovery of an unstable, temperamental or severely depressed patient. The surgeon should always disclose the full facts to the immediate family and gain help in these dangerous and delicate cases from their knowledge of the patient's reaction patterns. In the ordinary case there is no such warrant for suppressing facts and the surgeon must make a substantial disclosure to the patient pre-operatively or risk liability in tort."<sup>2</sup> This proposition, proffered casually without discussion, caught the eyes of lawyers who had been confronted with just such cases in their practice and led both to exchanges of correspondence and to a determination of the writer to probe the subject further. Later he was able to recruit Dr. Charles C. Lund, a leading Boston surgeon with a large experience in the treatment of cancer, to discuss the obligation of the medical man to tell his patient the whole truth about his disease or condition when full disclosure would be likely to produce great mental shock and bad effects on treatment. Every lawyer and judge must, I think, recognize that Dr. Lund's views are guided by the highest sense of obligation to the patient and by humanitarian motives, and his excellent discourse should go far toward putting this difficult problem of ethics, medicine and law upon those grounds which should control its solution. The present note is no rejoinder to Dr. Lund's excellent dissertation, but rather an effort to predict how far courts of law may safely and reasonably recognize that a physician has a therapeutic privilege, in select cases, to withhold the full diagnosis from his patient.

Anglo-American law starts with the premise of thorough-going self determination: it follows that each man is considered to be master of his own body, and he may, if he be of sound mind, expressly prohibit the performance of life-saving surgery.<sup>3</sup> A doctor might well believe that an operation is

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medically desirable or necessary, but the law does not permit him to substitute his own judgment for that of the patient by any form of artifice or deception. A surgeon who reported to the patient that he intended to undertake minor repairs of her cervix, was held liable in damages for completely removing her uterus and reproductive organs, a purpose he had decided upon in the beginning, on therapeutic grounds, but had executed without disclosing his intention. The court held there was no adequate consent to the surgery in question.<sup>4</sup> The fact is that the physician-patient relationship involves an element of trust and confidence, and obligations of good faith require the surgeon to make the fullest possible disclosure concerning risks of any proposed action which may result in injury to the patient. In the case of *Kinney v. Lockwood Clinic Ltd.*,<sup>5</sup> the plaintiff, an adult female, had gone to her surgeon complaining of a swelling in the palm of her right hand. The defendant diagnosed it as a Dupuytren's contracture and recommended corrective surgery without disclosing to the patient the considerable risk that the operation might fail, leaving plaintiff's hand worse than before. The patient submitted to the operation which, according to the evidence, she would not have done had she known the odds of failure. The operation was skillfully performed, but failed to achieve the expected result and the patient was left with a greater disability than she had originally. She then sued the surgeon for damages. A jury awarded her \$1,000 and on appeal a judgment in plaintiff's favor for this amount was upheld on the ground that even though the operation was skillfully performed, the defendant had breached his duty to make a full disclosure of the surgical risk to the patient as an incident to gaining her enlightened consent.

It is against this background of acknowledged law that the present problem must be projected. The writer believes that, in general, no medical privilege should be recognized to withhold the diagnosis in ordinary cases where the usual patient would feel entitled to have the information as a basis for charting his course, there being no apparent grounds for supposing that a disclosure of the truth would engender in the patient reactions dangerous to his health or life. If a broad, absolute privilege were granted to the physician to withhold medical information on allegedly therapeutic grounds, this would afford a perfect shield to cover the negligence of many who were unable to reach a timely or accurate diagnosis of the true illness. The physician could always say that he knew the diagnosis but withheld it for fear of worsening the patient's condition. Secondly, it would be dangerous in the extreme to say that a physician is entitled, either by misrepresentation or concealment, to gain the patient's consent to particular forms of treatment on the theory that "the doctor knows best" and it would only make the patient a sicker man to hear the risks.

It is not to any such unlimited scope of authority or action that Dr. Lund's remarks are addressed, and the writer has taken pains to deny the desirability of such a broad privilege in order to anticipate objections and to delimit the scope of the present discussion. The writer strongly believes

that the physician should be recognized to have a therapeutic privilege to withhold part or all of the facts regarding a dread illness, when he has reason to believe that communicating them freely to the patient will involve risks of causing his death or serious impairment of his health without any counter-vailing gain. It is suggested that this should be in the nature of an imperfect privilege, to be passed upon by the presiding judge in the light of evidence adduced in the particular case. It now devolves upon us to consider the legal foundation for such a privilege and to discriminate significant cases in which it should and should not be applied.

So far as the writer knows, there is little or no legal authority bearing upon the existence of such a privilege. The question was raised, to some degree, however, in the early Massachusetts case of Twombly and wife v. Leach,<sup>6</sup> an action on the case against a physician for alleged malpractice in treating a felon of the thumb and consequent lymphangitis which plaintiff's wife developed after accidentally inflicting a penetrating wound upon herself with a paring knife. It appeared that defendant treated her for a considerable time without disclosing the diagnosis. On the trial of the case, the court refused to permit defendant to ask several expert witnesses: "whether or not it is good medical treatment in some cases to withhold from the patient the extent of the disease and her actual condition?" The jury returned a verdict in plaintiff's favor in the trial court, but on appeal defendant's exceptions were sustained and a new trial was granted on the ground, among others, that "upon the question whether it be good medical practice to withhold from a patient in a particular emergency; or under given or supposed circumstances, a knowledge of the extent and danger of his disease, the testimony of educated and experienced medical practitioners is material and peculiarly appropriate."

The one sovereign question by which one may fairly test the obligation of the physician is this: considering the nature of the particular physician-patient relationship, or of the employment, would the withholding of the specific diagnosis defeat the patient's just expectations or would this, under all the circumstances, really contribute to a successful performance of the physician's mission in the case?

We propose to take up in succession, two totally different cases, as follows: The situation presented when the patient comes to the physician to gain the advantage of a diagnosis for informational purposes only, and the situation where he resorts to the doctor for medical treatment, the diagnosis being incidental.

1. *Duty of a physician in respect to a patient who employs him for the express purpose of finding out "the worst possible facts" about his malady, usually as a basis for arranging personal affairs.*

We must recognize the fact that circumstances may arise where it is of great personal moment to an individual to know approximately how long he has to live and what the state of his health will be during that time. This information may be of incalculable value to a business executive or to a per-

son with many diverse interests and investments which must be brought in hand within his remaining period of activity if his family is not to suffer. Such an individual may well have been under medical treatment previously and suspect that he has a fatal disease. In coming to the particular specialist, he is asking for a precision diagnosis and prognosis. The physician must undertake to decide for himself whether or not the individual can really stand to learn the truth and whether he, as doctor, is content to accept employment on the terms stipulated. One course open to the doctor is to refuse employment, for it is well settled law that a physician may decline, even arbitrarily, to engage his services.<sup>7</sup> If the doctor is to proceed, he must realize that the giving of information has been made the essence of his engagement and any negligence in diagnosis, any suppression of facts or concealment would entail not only a breach of his professional engagement but an abuse of trust. Furthermore, the law is clear that undertaking such an assignment involves the practice of medicine, even though there be no intention to apply treatment after establishing the diagnosis and giving information. This being true, the duty of the doctor attaches at the time he enters upon the undertaking, without reference to whether he is paid for the service or not. Liabilities arising from the practice of medicine sound in tort rather than in contract, although the relationship may have been introduced by a formal employment. Thus, in *Harriet v. Plimpton*,<sup>8</sup> a Massachusetts case which arose at the end of the last century, a physician was requested to make a pre-marital examination to determine whether a prospective bridegroom, the plaintiff, had venereal disease. He negligently diagnosed the young man as having gonorrhea, when in fact, he had no such disease. This diagnosis, being communicated to the family of the intended bride, caused the engagement to be broken off and for this injury the plaintiff sued the defendant physician in tort and recovered damages. The Supreme Judicial Court of Massachusetts affirmed the existence of liability. In the interesting Oregon case of *Guisti v. C. H. Weston Co.*,<sup>9</sup> the defendant physician examined a football player to determine whether the fact of previous injuries rendered him unfit for further participation in the sport. As the result of a negligent diagnosis he authorized the football player to play and the latter suffered a serious injury. It was held that the defendant physician was liable for this injurious consequence of his negligent diagnosis. Further examples of legal liability for negligent diagnosis, despite the absence of any intention to treat the patient, are afforded by those instances where a medical examiner's negligent diagnosis causes him to issue certificates of lunacy, thus bringing about commitment of the plaintiff, a sane individual, to a mental institution. Both American and British courts recognize that the plaintiff, in such a case, may have a right of action for damages for injury resulting from the negligent diagnosis.<sup>10</sup> It is thus evident, both on reason and on authority, that the loose statement sometimes made that "there is no legal liability for negligent diagnosis unless followed by negligent treatment" is incorrect; in many instances the doctor's diagnosis is solicited for informa-



tional purposes only and erroneous conclusions may cause various sorts of legal injury to the relying party.

It is generally acknowledged that very few people have that degree of self possession or scientific detachment which is needed to prepare them for news of their own impending death. Consider two contrasting cases. It is common knowledge that Dr. Hans Zinsser, the great bacteriologist at Harvard, was carried away in late middle age by a malignant disease for which medical science had no cure. Dr. Zinsser suspected that he might have fallen victim to such a disease and medical confirmation of that fact meant that he had approximately one year to live before he might expect the curtains to be lowered on his very full and interesting life. It is said by those who knew him that his knowledge that the days of the year were the last he would ever see gave them a very special meaning and exquisite value. It was during this time that Dr. Zinsser wrote his book (generally considered an autobiographical sketch) entitled "As I Remember Him."<sup>11</sup> Here, then, was the case of a man who needed notice to put his affairs in order, who had at the same time the philosophic composure to accept the inevitable facts of approaching death.

2. *Duty of the physician where his primary engagement is to treat the total personality of the patient, the diagnosis being secondary to that end.* It is but rarely, however, that the doctor is engaged for the express purpose of supplying a precision diagnosis and prognosis in regard to presence of malignant disease and likelihood of early death. As a rule, the patient's cancer will cause symptoms referable to some area of the body or some organ and he will come to the doctor for purposes of treatment. Sudden disclosure of a dread disease may cause tremendous repercussions in the patient. The writer recalls the case of a young woman who went to a physician on the eastern seaboard, complaining of symptoms which led him to suspect syphilis. A positive blood Wassermann reaction confirmed the diagnosis and he revealed the fact to the young lady at a morning conference without taking proper pains to explain that such a disease may be innocently contracted and that modern drug therapy now enables the dread effects of the malady to be circumvented. The young lady went home and promptly committed suicide. In another case, the story goes that a leading Boston surgeon realized his gastric complaint must be due either to cancer of the stomach or a mere ulcer. He submitted to surgery and afterwards asked the friend who performed the operation: "John, was it an ulcer?" "No, it was not an ulcer." Nothing more was ever said by either concerning the true diagnosis. The case illustrates the fact that even medical men sometimes prefer to avoid too frank a discussion or recognition of malignant disease which is destined to end their own lives. To tell the patient the truth and the whole truth often causes violent psychological reactions in the patient and an undermining of morale without any countervailing gain. In the ordinary case, it may indeed be negligent medical practice to worsen the patient's condition and to destroy or impair his chances of recovery by such

injudicious disclosures. While it is true that a physician has a duty to use due care in bringing about the cure of the patient, it would seem that an even more primary duty is to use care in seeing that he does not make a patient who needs surgery inoperable, or a medical patient untreatable, by tearing down the fabric of his psychic resistance.

The most crucial question raised by Dr. Lund's discussion is whether operation performed after only partial disclosure of the true condition, can be justified legally. Assuming the presence of a dread disease such as cancer, we believe the answer is yes, provided there is no fundamental concealment or misrepresentation as to the general nature or extent of the surgery to be done. It is not defensible, as we have seen, for a surgeon to represent that he intends to perform a repair of a woman's cervix and then avail himself of the opportunity to remove her entire reproductive organs. But if he tells the woman that he will be required to remove her breast and certain tributary lymph nodes, he has accurately described the nature of the proposed operation and gained her consent to the anatomical loss involved. The only withholding of facts has been in respect to the reason, and this, as we have seen, can be justified in special cases, on therapeutic grounds.

To illustrate, the writer might cite an actual case which arose in one of the western states in respect to which he was asked to give an opinion. Taking care to substitute fictitious names, we may summarize that case as follows: A Mrs. Brown, who had a lump in her breast medically recognizable as cancer, went to a reputable surgeon in a rather distraught frame of mind. At the beginning of the interview she told surgeon Jones that if she had cancer she would commit suicide. Because of the psychological condition of the patient, and her threat of self destruction, the surgeon told her that she had a breast tumor and recommended mastectomy (removal of the breast and tributary lymph glands). This operation was successfully performed with the result that a highly dangerous form of early cancer was eradicated. Subsequently, however, Mrs. Brown discovered that surgeon Jones concealed from her the fact that she had cancer and she brought an action against him for malpractice, alleging further that since her consent to operation was gained by fraud it was not effective, so that an unauthorized operation had been performed upon her which involved a battery. An opinion was sought from the writer as to the legal bearings of the particular problem. In reply, the writer took the position that there was no breach of medical duty to the patient because her own threats of self-destruction if she learned she had cancer raised a therapeutic privilege to withhold the true facts in treating her case. Secondly, the writer called attention to the fact that any plaintiff, whether the action be for malpractice or otherwise, is required to produce substantial evidence showing duty, dereliction, direct causation (proximate causation) and damages (injury) before he can fulfill the requirements of the liability formula and hold the defendant in damages. It was urged that Mrs. Brown would have an almost impossible task of proving actual damages, for she was still alive two years after the operation, whereas

medical men would agree she could have been expected to die before the end of that time had her cancer not been effectually treated. On that proposition, the case of *Stoffberg v. Elliott*, a South African case, was cited as pertinent.<sup>12</sup>

When the case in question came to trial, attorneys for the defendant, surgeon Brown, developed both theories vigorously. The trial court instructed a verdict in the defendant's favor, thus achieving by judicial intervention the same result as that reached by the jury in the *Stoffberg* case.

We must remember that in the difficult category of cases we are considering, the patient himself goes through a gradual metamorphosis of mental attitude toward his illness. He starts with the enthusiastic belief that he will soon be on his feet again. Such a spirit has direct therapeutic value and will help bring about a cure if a cure is possible. If the case be incurable, the patient will gradually see that he is not getting better. Next, he realizes that he is not going to get better. The last step in this mental process is to draw the inference that the disease is a fatal one. An insight gained gradually in this way is less likely to cause intense mental anguish than knowledge gained abruptly of one's imminent demise. There is another principle to be borne in mind from a legal point of view: in all such cases, the physician should make it a practice, wherever possible, to communicate the true facts immediately to near relatives. This will enable special arrangements to be made in respect to financial affairs, property matters or family dispositions, almost as effectually as if the individual himself knew the truth. Finally, it would seem that the attending physician, in late stages of such a malady, should do what he can to assure the patient of a chance to make a last will and testament and to have the solace and comfort of religious ministrations. If a physician conducts a case of dread or malignant disease in such a manner, it is not thought that any court in the land will find that he has been guilty of any dereliction; the law will add its seal of approval to the opinion of the medical fraternity that he has acted for the best.

If a well oriented patient, who has become adjusted to his illness, confronts the doctor with a frank question as to the eventual prognosis, it is thought that the doctor should come as near to telling the truth as appears defensible, but it is believed that how he may best discharge his obligation to the patient in this difficult situation should be considered to involve primarily a question of medical judgment. His choice of plausible courses should not be called into question if it appears, all circumstances considered, that the physician was motivated only by the patient's best therapeutic interests and proceeded as some competent medical men would have done in a similar situation even though other competent practitioners would have done the opposite.

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12. *Stoffberg v. Elliott* (Sup. Ct. South Africa, C. G. H., P. D., 1922) S. A. Law Reports (1923), C. P. D. 148. In that case, defendant was a visiting surgeon and he amputated the plaintiff's penis for advanced cancer, supposing that the hospital had procured pre-operative consent according to its usual routine. Through an oversight it had not done so and the patient sued the surgeon for assault and battery, seeking £10,000 in damages. According to the medical testimony, the plaintiff would have died a horrible death in less than two years had surgery been withheld. The trial court rightly held the operation was a battery, even though the surgeon acted bona fide under a mistaken belief that consent had been given. The judge, however, instructed the jury that they were entitled to say whether plaintiff had suffered any damage at all. Under the charge given, the jury returned a verdict for the defendant.

The point is so important that we consider it worthwhile to reproduce the charge which the trial judge delivered to the jury, this being as follows:

"Lastly, if you think there was cancer and you think this operation was necessary to save his life, then you have still further to consider whether he suffered any damage at all. That is a matter which I will leave entirely to you. You have heard all the evidence as to the nature of cancer, and what it leads to, and you have heard the evidence of Dr. Hamman, for the plaintiff, who said that if a man had cancer of the penis he would be very much surprised if he were alive after two years time. You can take that as admitted, the evidence having been given for the plaintiff. Well, the operation was performed in March of this year, and, if he would have been dead in two years, and if his death would have been such a horrible thing as described, then has he suffered any damage by having his penis removed? That seems to be the most difficult question in the whole case. If you think he has suffered no damage at all then you are justified in giving judgment for the defendant; if you are satisfied he had cancer and this was the only thing to save his life, and you still think, in spite of that, that he suffered damage, well, then you must attempt to assess the damage which he has suffered, and you must give judgment for the plaintiff for that amount of damages."

"That the operation was necessary is a circumstance usually allowed in mitigation of damages in an action for unconsented operation. See Restatement, Torts (1939) Sec. 920."

# OBSERVATIONS ON TUBERCULOSIS CONTROL IN A UNIVERSITY HOSPITAL\*

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THE early diagnosis of pulmonary tuberculosis is fundamentally a clinical problem. Though the first steps in case-finding, which consist of tuberculin testing and roentgen-ray surveys, may be viewed as technics of public health administration and roentgenology, the evaluation and management of the suspected or manifest disease found is the responsibility of the clinician. Despite this self-evident fact, in many teaching hospitals relatively little attention is given either to adequate measures for control of tuberculosis among their personnel, or to the training of students and staff in the modern concepts of early diagnosis and treatment. Even where periodic roentgen-ray examinations of students, nurses, and physicians are established routine, unnecessary, and sometimes dangerous, delays in instituting treatment still frequently occur because of faulty clinical evaluation. A well-planned, continuous case-finding program nevertheless offers valuable means of familiarizing not only medical students, but all levels of the clinical staff, with the contemporary concepts of the management of this disease. Although pulmonary tuberculosis still merits from teachers of medicine the attention so abundantly bestowed on it by Osler,<sup>1</sup> the teaching centers which effectively integrate the clinical study thereof with other branches of internal medicine are few.

Since the introduction of modern case-finding methods the early detection of tuberculosis has been the subject of much investigation. The pioneer observations, however, of Heimbeck in Europe, and Myers, Opie, Soper, and Amberson in this country, relative to tuberculosis among nurses and medical students, have not generally received from internists and teachers in university hospitals the attention their importance deserves. Academic interest in tuberculosis has declined as a natural consequence of our modern recognition of the public health aspects of the disease and the growth of special institutions for its treatment. These are predominantly tax-supported, and connected loosely, if at all, with the centers of medical education organized around general hospitals. Because many of these hospitals still exclude patients with known tuberculosis, teachers of internal medicine have often lacked opportunity to develop judgment and skill in the clinical recognition and evaluation of the disease. Yet inevitably these hospitals have tuberculosis problems since they are staffed largely by young and middle-aged adults

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of the age periods in which tuberculosis exacts its greatest toll. Moreover these problems exist whether they are appreciated or neglected, and regardless of whether or not there is a recognized hazard from open cases of pulmonary tuberculosis knowingly admitted. Because of the technics now available for early tuberculosis case-finding the teaching staffs of university hospitals have opportunities unparalleled in the past, or in the study of most other diseases, for practicing and teaching preventive principles in clinical medicine. The following observations are based on experience with pulmonary tuberculosis among professional students and personnel in a large university hospital.

### I. PRÉVALENCE OF TUBERCULOUS INFECTION AND OF PULMONARY TUBERCULOSIS IN PROFESSIONAL STUDENTS AND PERSONNEL

A continuous case-finding program among medical students and student nurses, first undertaken in this institution in 1932, was reorganized and extended to include other professional groups in 1939. The earlier experience has been previously reported.<sup>2</sup> The statistics presented below pertain to the five year period from July 1, 1939 to July 1, 1944.

#### TUBERCULIN TESTS

A schedule of periodic tuberculin tests was limited to the undergraduate medical and nursing students. The high turnover in the composition of other professional groups, such as graduate staff nurses, postgraduate student nurses and medical house staff, did not permit a practicable schedule of periodic skin testing and retesting among them. Nor is this method of as much practical or epidemiologic importance among these older groups, in which the great majority may be expected to show positive tuberculin reactions. Such, at least, has been true in certain segments of these groups which have been tested both in earlier and recent years.

The undergraduate students were tested at the beginning of their course by the standard two dose method of Mantoux. To permit comparison with the earlier data Old Tuberculin was retained as the testing material, 0.01 mg. being used for the first dose and 1.0 mg. for the second dose. When a doubtful reaction was produced by the first dose an intermediate dose of 0.1 mg. was given to guard against severe reactions. Those students whose skin reactions to the final dose of 1.0 mg. were negative or doubtful were retested every six months until a positive reaction was noted or, finally, within a month before graduation.

Figures 1 and 2 show graphically the observations on the tuberculin reactions of medical and nursing students, respectively, in both the earlier and later periods. There has been a conspicuous decline in the number of positive reactors among the entering classes in the last five years. The potency of the tuberculin used has been checked by various methods, both in the laboratory and clinically. These methods have included simultaneous con-

trol tests with first and second strength Purified Protein Derivative which showed no significant variation from the tests made with Old Tuberculin. There is no doubt, therefore, of the accuracy of the observations.

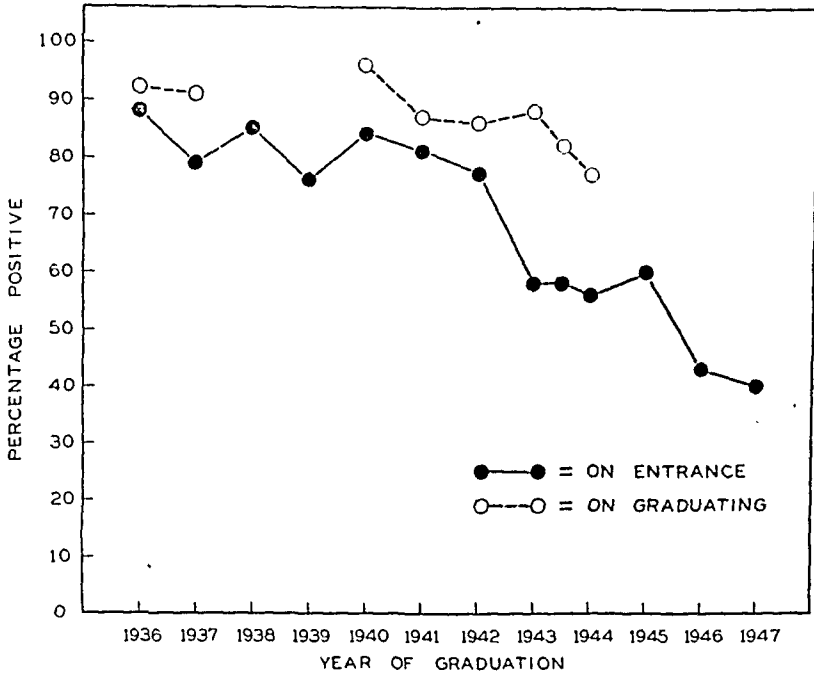


FIG. 1. Tuberculin reactions in medical students.

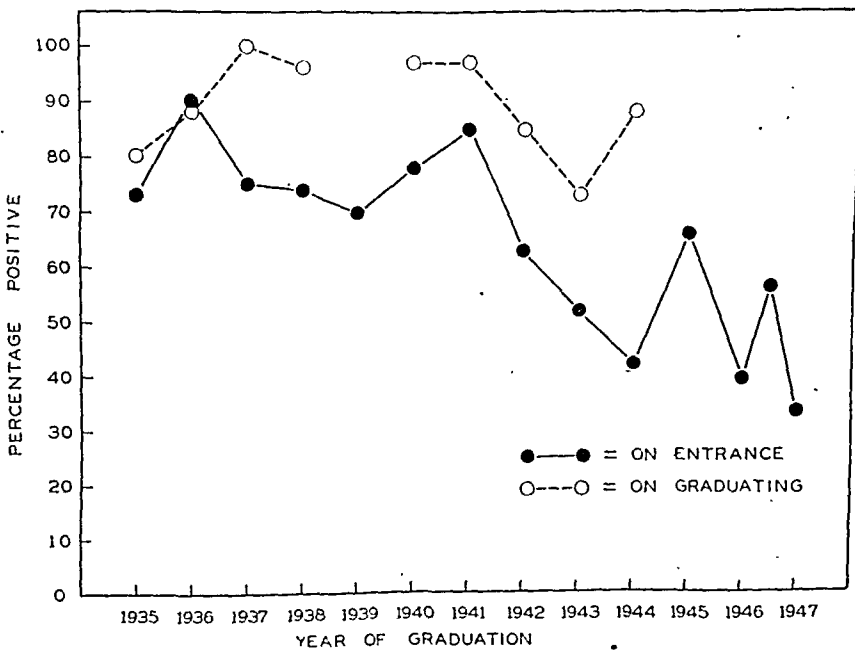


FIG. 2. Tuberculin reactions in student nurses.

## CASE FINDING PROGRAM

The professional groups included in the continuous periodic chest roentgen-ray program consist of the undergraduate medical and nursing students, graduate staff nurses, postgraduate student nurses and medical house staff. All members were required to have routine chest roentgen-ray examinations on entrance and annually thereafter. Among the undergraduate students routine reexaminations were scheduled at six month intervals in those instances in which the tuberculin reaction was originally negative and became positive in any of the semiannual retests. Interval examinations between the regularly scheduled routine examinations were ordered freely for persons in any of the groups when any clinical indication warranted. All roentgen-ray examinations were made in the standard manner on 14 by 17 inch celluloid film.

The number of cases of pulmonary tuberculosis diagnosed among the above-mentioned groups in the five year period is tabulated in table 1. Cases

TABLE I

Cases of Pulmonary Tuberculosis and Tuberculous Pleurisy Among Professional Groups Diagnosed in the Five-Year Period, July 1, 1939 to July 1, 1944

| Group                        | Number | Previously Diagnosed or Found on Entrance |      | Found After Prior Negative Roentgen-Ray |       | Pleural Effusion After Prior Negative Roentgen-Ray |       | Total with TBC |      | Rate New Cases per 1000 per Year |
|------------------------------|--------|-------------------------------------------|------|-----------------------------------------|-------|----------------------------------------------------|-------|----------------|------|----------------------------------|
|                              |        |                                           |      |                                         |       |                                                    |       |                |      |                                  |
| Medical Students             | 773    | 3                                         | 0.4% | 4                                       | 0.52% | 0                                                  | 0     | 7              | 0.9% | 2.0                              |
| Student Nurses               | 509    | 6                                         | 1.2% | 3                                       | 0.59% | 1                                                  | 0.2%  | 10             | 2.0% | 5.2                              |
| Graduate Nurses              | 2166   | 55                                        | 2.5% | 12                                      | 0.55% | 1                                                  | 0.05% | 68             | 3.1% | 6.0                              |
| Post-Graduate Student Nurses | 314    | 15                                        | 4.8% | 0                                       | 0     | 0                                                  | 0     | 15             | 4.8% |                                  |
| House Staff                  | 345    | 14                                        | 4.1% | 2                                       | 0.58% | 0                                                  | 0     | 16             | 4.7% |                                  |
| Total                        | 4107   | 93                                        | 2.2% | 21                                      | 0.51% | 2                                                  | 0.05% | 116            | 2.8% |                                  |

of tuberculous pleurisy with effusion, with or without demonstrable parenchymal foci, are included. There were no recognized cases of tuberculosis of other organs. All cases of arrested pulmonary tuberculosis, exclusive of calcified residues of childhood infection, are listed, as well as all cases diagnosed as active or probably active. The highest incidence of tuberculosis was in postgraduate student nurses. This is a group whose members remain for only four to eight months and who nearly all have graduated from other



training schools. Few of these nurses had ever had roentgen-ray examinations before, which may account for the accumulation of so many cases among them. The annual incidence of new cases, found after prior negative examinations, was calculated only for the undergraduate student groups and regular staff nurses.\* Too small a proportion of the postgraduate student nurses and the house staff remained for sufficiently long periods to permit calculation of annual rates for these groups. The distribution of cases according to the stage is shown in table 2. Although the ideal of establishing

TABLE II  
Distribution of Cases of Pulmonary Tuberculosis According to Stage of the Disease  
During the Five-Year Period, July 1, 1939 to July 1, 1944

| Group                              | Number | Total<br>with<br>TBC | Distribution<br>All Cases |                      |                 | Per Cent Diagnosed in<br>Minimal Stage—All Cases |                           |                |
|------------------------------------|--------|----------------------|---------------------------|----------------------|-----------------|--------------------------------------------------|---------------------------|----------------|
|                                    |        |                      | Minimal                   | Moderate<br>Advanced | Far<br>Advanced | After<br>Entrance                                | First<br>Examina-<br>tion | Total<br>Cases |
| Medical<br>Students                | 773    | 7                    | 5                         | 2                    | 0               | 75%                                              | 66.7%                     | 71.4%          |
| Student<br>Nurses                  | 509    | 10                   | 8                         | 2                    | 0               | 100%                                             | 66.7%                     | 80.0%          |
| Graduate<br>Nurses                 | 2166   | 68                   | 65                        | 3                    | 0               | 100%                                             | 94.5%                     | 95.6%          |
| Post-Graduate<br>Student<br>Nurses | 314    | 15                   | 15                        | 0                    | 0               |                                                  | 100%                      | 100%           |
| House<br>Staff                     | 345    | 16                   | 14                        | 1                    | 1               | 100%                                             | 85.7%                     | 87.5%          |
| Total                              | 4107   | 116                  | 107                       | 8                    | 1               | 95.6%                                            | 91.4%                     | 92.2%          |

all diagnoses at the minimal stage has not been reached, the proportion (95.6 per cent) among those who developed the disease while under observation approaches it, and even the overall percentage of 92.2 may be considered satisfactory. In this connection it should be mentioned that, exclusive of the cases of pleurisy without demonstrable parenchymal disease, there were

\* The annual incidence of new cases was calculated according to the modified life table formula as described by W. H. Frost (Am. Jr. Pub. Health, 1933, xxiii, 426) and suggested for this purpose by Barnwell and Beckerman (California and West. Med., 1943, lix, 1). The calculation of person years by this formula differs from that employed in our prior communication<sup>2</sup> wherein all exposure years were excluded which were not actual observation years concluded by a roentgen-ray examination. The difference in student person-years affects only the second significant figure in the final rate, so that the rate for the medical students in table 1 would be 2.1 instead of 2.0 per thousand per year, were the old method applied to the present data. The reason for changing to the Frost formula is to make the data comparable with those observed elsewhere. This formula provides a basis for comparison which has been conspicuously lacking from the literature on tuberculosis rates in hospital personnel. It must be emphasized, however, that rates so calculated represent only an approximation and that strict comparability is possible only if the annual turnover and the frequency of observations is the same in the groups which are to be compared.

only two which progressed to manifest symptoms before diagnosis. The others, regardless of extent, were all detected by means of the routine roentgen-ray examinations.

It is recognized that the schedule of roentgen-ray examinations has been one of minimal frequency and might not be suitable for other institutions, but for the conditions we have so far encountered the intervals have proved generally satisfactory. The statement which has been sometimes made that infiltrative lesions of tuberculous nature may appear and disappear within a year or even less is not in accord with our experience. Although this may occur it must be very rare and could not significantly affect the statistics of tuberculosis incidence in these groups.

## II. OCCUPATIONAL HAZARD AND METHODS OF CONTROL

Much has been written in recent years about tuberculosis as an occupational hazard for medical students, interns, nurses and other hospital workers. No attempt will be made to review this extensive literature, some of which tends to be alarmist and detrimental in its effect on the education of these same workers for the responsibilities that will be theirs in the diagnosis and care of the tuberculous. The purpose of this paper lies in attempting to formulate, on the basis of experience, what preventive measures in addition to a program of early case-finding are indicated. The situation in this institution may be considered a representative one. The New York Hospital is a thousand-bed hospital operated primarily as a teaching unit for the Cornell University Medical College, which adjoins it. Tuberculosis patients are not excluded, as they are from many voluntary hospitals, nor is there a large overcrowded tuberculosis service as is the case with many municipal hospitals. Various measures, revised from time to time, for the isolation of infectious cases and for the protection of students and attendants have been employed. All of the clinical teaching of medical students in tuberculosis is carried on in the hospital. The tuberculosis unit consists of 19 beds for open cases of tuberculosis and additional beds of unspecified number on a pavilion of 30 beds for non-infectious cases. A few tuberculous patients are kept temporarily on the surgical floors for pre- and post-operative care. While there, they are in single bed rooms. The protective measures now employed include the wearing of masks and gowns by attendants, washing of hands after contact with patients, and segregation of contaminated material. We regard it as impractical, if not actually misleading and detrimental to a proper professional attitude toward the patient, to impose a strict isolation technic of the kind employed for highly contagious diseases. Recent studies by Ordway, Medlar and Sasano<sup>3</sup> have shown that even prolonged sanatorium care and clinical stabilization of the disease for many months does not render the majority of patients strictly non-infectious if intensive search by the most refined methods is made for tubercle bacilli. Custodial care for such patients during the many years they may inter-

mittently discharge tubercle bacilli is neither available nor desirable. Nor can they join their families and become socially and economically rehabilitated and continue to live under a strict isolation regimen. Furthermore, if instructed in the principles of hygienic living they may resume their places in society without undue risk to their associates. It is therefore evidently unwise to place excessive emphasis on isolation but rather to begin in the hospital the education which will enable the patients to fulfill their own responsibilities toward the protection of others. Ideally, the general teaching hospital should not have to employ more elaborate methods of hygienic control than are customary and have over many years been found adequate in tuberculosis sanatoria. There is a special responsibility, however, with regard to the medical and nursing students, interns, residents and graduate staff nurses, a majority of whom fall into the young adult age group and whose physical welfare as well as educational opportunities are entrusted to the hospital. Statistics have been reported above which show a declining proportion of positive tuberculin reactions among successive entering classes of medical and nursing students. This is not an isolated experience and a similar trend has been reported from other communities. There is reason to believe that young adults, particularly those who have not had a first infection in childhood or adolescence, are more likely to develop progressive disease if exposed than are older persons. Our own cases among medical and nursing students have been mostly, though not exclusively, found among those who were tuberculin negative on entrance. Such relationships, indicating higher prevalence of clinical disease in original nonreactors, have been reported in most similar studies of tuberculosis in students and nurses. There have been some exceptions to the rule and a clear demonstration of these epidemiologic factors must await completion of larger scale surveys. There is sufficient evidence to justify the use of somewhat extraordinary precautions for these young people, especially in view of the trend noted toward a declining tuberculinization of the general population. We have for this reason hesitated to recommend the discontinuance of a mask and gown technic. Our observations, like other tuberculin surveys of medical and nursing students, indicate a more rapid annual increase in the percentage of positive reactions than the 1 per cent per annum reported by Myers<sup>4</sup> and his co-workers for a general university population. This has been emphasized by the Minnesota investigators as evidence of the existence of a special hazard for medical and nursing students. Though some of the relative acceleration of infection in our medical and nursing student groups may be attributable to metropolitan conditions, it is probably due in part to occupational factors, since the students spend the major portion of their waking hours in the institution. The acquisition of infection, however, though it is the sine qua non of progressive disease, is not in the majority of instances followed by clinically important tuberculosis. Moreover, it is not likely to be escaped indefinitely, especially by anyone exercising the functions

of physician or nurse. Our results in tuberculin testing of certain groups of newly appointed staff nurses, mostly graduates of other nursing schools, have revealed 80 to 90 per cent infected. These are predominantly recent graduates and mostly in the third decade of life. Furthermore, the annual increase among the students is attributable at least in part to contact with the unsuspected open cases which are encountered in any department of a general hospital, rather than exclusively or even predominantly to service in the tuberculosis unit. We do not accept the rate of acquisition of infection as a definitive criterion of conditions relative to the tuberculosis hazard. More important is the incidence of actual progressive or potentially progressive disease. Here again our expectations cannot be for complete prevention but rather for control, insofar as is consistent with exercise of the functions of a hospital staff in the care of the sick and of students in their acquisition of professional competency.

#### COMPARATIVE INCIDENCE

The rate of 2.0 per thousand per year (table 1) for the medical students is no higher than the published rates for male clerical employees of the Metropolitan Life Insurance Company, among whom Reid<sup>5</sup> calculated 2 to 3 per thousand per year in the comparable age group 20 to 29. A similar rate of 2 to 3 per thousand per year was also reported among female clerical employees in the age group 17 to 34. We have not tabulated the age distribution of our graduate staff nurses but the great majority are within these limits, as are all of the undergraduate student nurses. When the rates of the nurses are corrected to exclude pleurisy without demonstrable parenchymal tuberculosis, cases of which are not included in Reid's statistics, the figures are 3.8 and 5.6 per thousand per year for student and graduate nurses respectively. The comparison is therefore not so favorable for the nurses as it is for the medical students, the former showing an incidence approximately twice that of the clerical workers. Unpublished data, moreover, indicate that the differential may be even greater, since Reid's 1940-1944 estimates indicate a considerable decline from the published 1930-1939 statistics.<sup>6</sup> It must be emphasized that this is merely a rough comparison since neither the case finding routines, the annual population turnover, nor the method of calculation were exactly the same. It appears reasonable to conclude, however, that a significantly, though not alarmingly higher incidence of tuberculosis prevails among both student and graduate nurses than among clerical workers. The medical students seem to have an incidence approximately the same as expected, without the influence of any factors of occupational exposure.

Comparison of this experience with the results of similar studies from other hospitals indicates that our rates for the nursing students are lower than those reported by Riggins and Amberson<sup>7</sup> and those reported by

Beckerman,<sup>8</sup> which were 1.93 and 1.22 per hundred per year respectively.\* There are few other studies reported in which the incidence among student nurses is calculated on a person-year basis or in which data are given which permit such calculation. With respect to medical students and graduate nurses there are apparently no reports of other than crude incidence rates, and in the case of the graduate nurses there are very few even of these. There exist, therefore, no data with which we can compare our experience in respect to these two groups.

The higher tuberculosis rates among medical college graduates than among law school graduates reported by Myers<sup>4</sup> may well be due in part to a greater likelihood of diagnosis in the former. In any case, earlier diagnosis appears to have neutralized the greater incidence, for the death rates are not significantly different. In this connection it should be emphasized that statistics of incidence among medical and nursing personnel, derived from case-finding programs, are indicative of potentially serious rather than of permanently disabling or fatal tuberculosis. If recognized early and treated promptly, there may be a lower death rate and a lower rate of advanced disease even where there is a higher total incidence of cases. The more serious cases in students have usually been among those found on the first examination of newly enrolled students. In former years, before a methodical case-finding program had been extended to include graduate nurses and house staff physicians, an excessive proportion (25 per cent among the nurses) of tuberculosis was not diagnosed until the disease had advanced beyond the minimal stage and some of those have since died. Among those diagnosed in the past five years including all groups in the program, there have been no known deaths and only nine cases (table 2), exclusive of previously known and treated patients accepted for rehabilitation, had reached a moderately advanced stage when treatment was instituted. Eight of these were diagnosed in newly enrolled students or staff.

#### HAZARD IN TUBERCULOSIS WARD

Various attempts have been made to estimate the hazard of infection offered by work on the tuberculosis ward. Each student nurse spends a month on the service during her period of training. The number of those originally tuberculin negative, whose test became positive within three months after working on the tuberculosis pavilion, was contrasted with the number who became positive within the same interval after work on the Pediatrics Service. The latter was chosen because, of all the services in the hospital, there are least likely to be patients with a positive sputum on its wards. The rates were found to be almost identical for both services, indicating that a change in reaction when it occurred was without relation to

\*An increase in the rate among the nursing students of this institution has become manifest currently since the close of the five year period on which the statistics of the present communication are based. Whether this will materially affect the incidence in the next full five year period and make it more nearly approach those cited from other institutions is not yet evident.

the type of service. In order to ascertain the possible relation of service on the tuberculosis ward to the development of clinical tuberculosis, as opposed to the mere acquisition of infection, an analysis was made of the cases of pulmonary tuberculosis in graduate nurses with respect to the departments of the hospital in which they worked. From the opening of the hospital in 1932 until 1941 there had been 57 cases of pulmonary tuberculosis diagnosed in graduate nurses of which 24 might have acquired their disease in the hospital, as they either had negative initial films or none at all. Five of the cases developed among the staff of the tuberculosis pavilion. Although two of these could have had no causal relationship with their work on the service, it was thought that it was still an excessive proportion of the total of 132 who had been employed there. Therefore, in 1941 a rule was made that for regular employment in this service only nurses would be selected who were over 25 years of age and whose tuberculin test was positive. Since then, in over three years, there have been no graduate nurses assigned to this work who have subsequently developed tuberculosis. Although the above-mentioned regulation has occasioned some difficulty in nursing administration and in finding prompt replacements for nurses who may resign, it is seemingly proving successful. Temporary assignment of younger student nurses, even with negative tuberculin tests, has nevertheless been permitted as an essential part of their training.

#### HAZARD IN GENERAL WARDS

The significant incidence of unsuspected tuberculosis among patients of general hospitals has been recognized only recently. The application of routine chest roentgenography to all patients entering a hospital either as in-patients or as out-patients is the next important step which should be taken in the control of tuberculosis within such institutions. It has been done on a demonstration basis in several large hospitals and has been found practicable and highly rewarding. The newer technics of low-cost fluoro-roentgenography will make this not only a possibility but an obligation for all hospitals within the very near future. This development will in itself increase the interest and the responsibility of the internists and clinical teachers with respect to tuberculosis, which has too long been regarded by many as principally a problem of custodial care. They will be called upon to make the clinical evaluations and will have the opportunity more frequently than has been afforded in the past of observing the behavior of the disease in its earlier phases when the most important decisions must be made. If these are made correctly there will be the double advantage of benefiting the patients and indirectly protecting their associates by recognition of possible immediate or future sources of infection. If they are made incorrectly there will have been engendered a false sense of security and the examinations were better not made. The tuberculosis sanatoria are crowded with advanced cases, many of which have had routine roentgenograms in the past demonstrating lesions which were missed or clinically misinterpreted.

### III. CLINICAL EVALUATION OF PULMONARY INFILTRATIONS

It has been emphasized particularly by Amberson<sup>9</sup> that minimal tuberculous pulmonary infiltrations in young adults are to be regarded as potentially progressive until proved otherwise. Our experience has repeatedly confirmed the correctness of this viewpoint. We have been particularly impressed by the capacity of early infiltrates, sometimes of such small extent as to be easily overlooked or regarded as doubtful, to spread rapidly. When such sudden extensions occur they are usually not heralded by any premonitory symptoms. They occur most often in newly established foci but may develop from infiltrations which have existed with little or no change for a year or more. The following cases are illustrative of such instances.

*Case 1.* D. L., a senior medical student, was admitted to the hospital from the Student Health Service on March 2, 1942.

The present illness, as determined by retrospective examination of a series of roentgenograms and the record of tuberculin tests, apparently began asymptotically in 1940. Mantoux tuberculin tests had been negative to 1.0 mg. O.T. on entrance to medical school in 1938 and on subsequent semi-annual retests until October 1940 when the reaction was positive for the first time. Routine roentgenograms in 1938 and 1939 had been negative. A routine film in November 1940 (figure 3A) showed a suspicious area behind the anterior portion of the left first rib. This was checked by another film in December 1940 which was regarded as not confirmatory of the suspected lesion. In May 1941 a routine roentgenogram again was regarded as suspicious and the patient was now carefully studied, utilizing special oblique views, physical examination, gastric washings, and erythrocyte sedimentation rate. None of these procedures confirmed the presence of an active lesion or even of a definite focus. Because the roentgen-ray shadow was not regarded as definite the patient was now classed as an observation case and was closely followed with periodic roentgenograms and sedimentation rate determinations. No change was noted in the serial roentgenograms, the patient remained asymptomatic, and the erythrocyte sedimentation rate normal in the periodic check-up examinations up to within one month of the onset of his symptoms. These began two weeks before admission and consisted of cough, malaise, chilliness and fever. On admission to the hospital the temperature was 101° F. There were physical signs of pulmonary infiltration at the apex of the left lung, and the roentgenogram (figure 3B) showed a moderately advanced dense exudative process in the region above the third rib on the left. The sputum was positive for acid-fast bacilli.

The patient's course was characterized by continued cough, expectoration, and fever ranging up to 101° F. for the first two weeks, after which on a regimen of strict bed rest there was symptomatic improvement. Before transfer to a sanatorium in June, 1942 there had been considerable resolution and the sputum had become negative on concentration. By December 1943 after one and a half years of sanatorium treatment a remarkable amount of resolution had taken place and the residual infiltration was of such small extent as to be scarcely visible.

*Comment:* This case illustrates strikingly the difficulty of establishing a definite diagnosis of an early infiltrate when this is situated near the apex of the lung in the region of closely overlapping bony structures. Retrospectively, there can be little doubt that such an infiltrate was already present in November 1940, nearly one and one-half years before the diagnosis was definitely established. It is also noteworthy that the sudden extension oc-

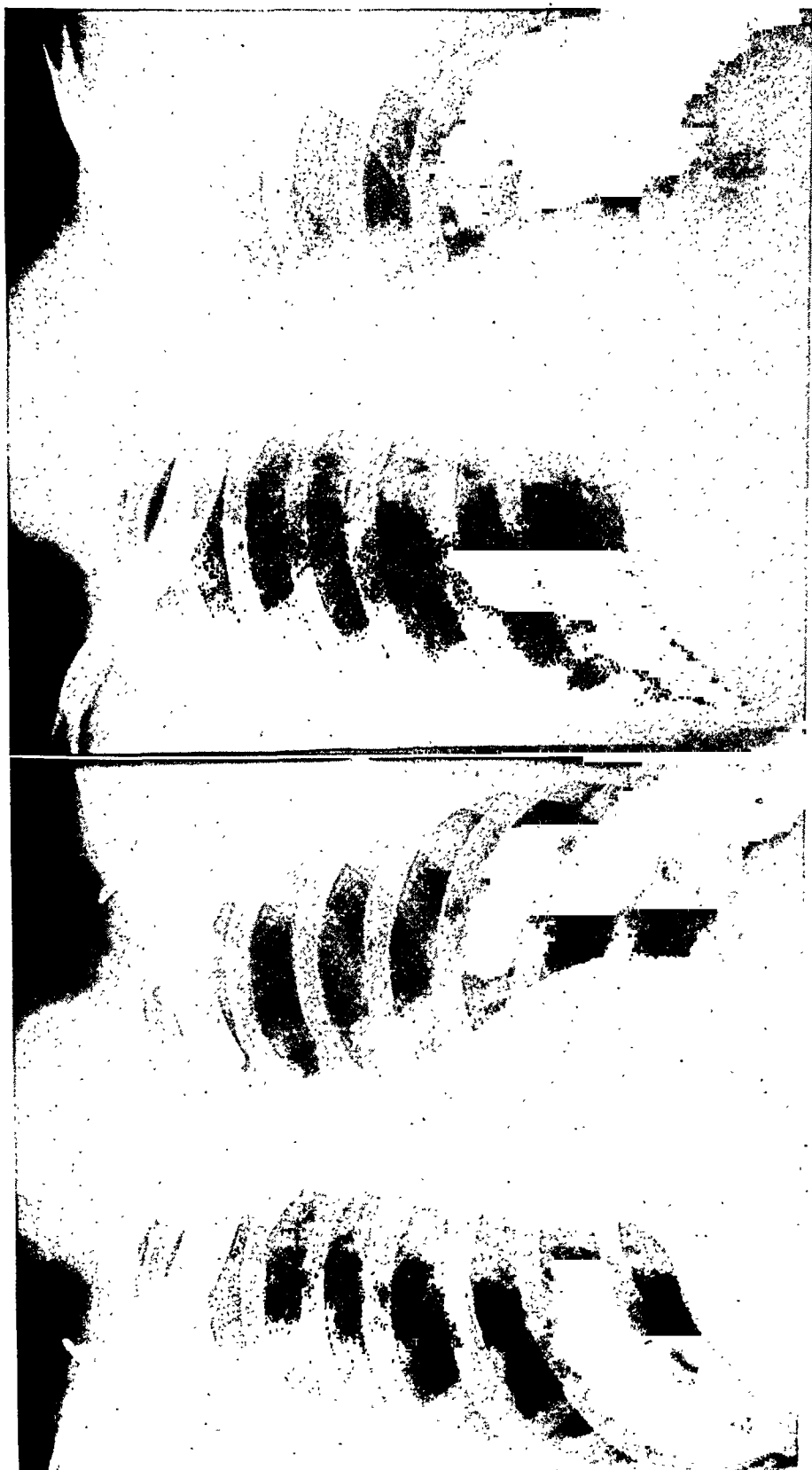


FIG. 3. Case 1. (a) Routine roentgenogram November 1940. Small infiltration behind first rib and in first interspace on the left.  
(b) March 1942. Spread of infiltration to involve upper third of left lung field.



curred characteristically without premonitory symptomatic, physical, or laboratory signs and that it did so after having remained roentgenographically unchanged and, indeed, so indefinite as to have been missed entirely by several experienced roentgenologists (and only regarded as suspicious by others and by several clinicians) for over a year.

*Case 2.* N. B., a 21 year old first year woman medical student, was admitted to the hospital on April 19, 1943 with chief complaint of hemoptysis. The present illness began asymptotically at least two years before this date as revealed by retrospective examination of a roentgenogram taken in college in 1941. This had been taken because of a family history of tuberculosis. It had been originally interpreted as negative but had been found on review to show a definite minimal infiltration in the middle third of the left lung. Another roentgenogram taken at college in the spring of 1942, a year before her entrance to medical school in April 1943 (war-time accelerated program), likewise shows the lesion. It was little changed in comparison with its appearance a year earlier. The disease had not been recognized at this time either. A routine physical examination four days prior to the initial hemoptysis had revealed no abnormal physical signs. The patient had been scheduled for her initial tuberculin test and chest roentgenogram in the Student Health Service but had not yet received either of these examinations, having matriculated within two weeks of the onset of her symptoms. The hemoptysis, of about 5 to 10 c.c. of pure blood, occurred less than an hour before the patient's admission to the hospital.

On admission the temperature was normal. The only abnormal physical signs noted were a few râles in the left infraclavicular region. Fluoroscopy showed a small area of infiltration in the middle third of the left lung together with an area of rarefaction of about 2 cm. diameter, interpreted as a small cavity. Within two hours of admission, and before a roentgenogram had been made, the patient had a second hemoptysis of about 400 c.c. and within the next several hours a series of further hemoptyses totalling another 500 to 600 c.c. Artificial pneumothorax on the left was now induced as an emergency procedure. There was no further bleeding until 24 hours later when the patient again had an hemoptysis of 200 c.c. Following this there was an abrupt rise of temperature to 103-104° F. and a roentgenogram showed consolidation of almost the entire lung. The high fever was sustained for four or five days, in spite of which the artificial pneumothorax was maintained. Sulfadiazine was also given, beginning on the fourth day, because of a leukocytosis of approximately 24,000. The temperature fell by lysis, reaching normal on the tenth day, and the sulfadiazine was discontinued on the following day after a total dosage of 33 grams. There was prompt resolution of the pneumonic process in the partially collapsed lung. After the pneumonia had cleared there was seen to be residual infiltration of limited extent, apparently in the upper part of the left lower lobe. No residual cavity could be made out. A small pleural effusion absorbed without thoracentesis and the patient was asymptomatic when transferred to a sanatorium two months after admission.

Sputum concentrates and gastric washings were negative before the patient's transfer but tubercle bacilli were found in the sputum in August 1943. The artificial pneumothorax was maintained until December 1943 when it was discontinued because of reappearance of a pleural effusion. A satisfactory reëxpansion was obtained and the patient was discharged from the sanatorium in January 1944 to continue a modified rest regimen at home. The disease was at this time apparently arrested.

*Comment:* This case, similar to the previous one, illustrates the explosive suddenness with which pulmonary tuberculosis may progress in untreated, symptomatically latent cases. The fact that a minimal lesion was present

as long as two years before the symptomatic onset emphasizes the consideration that treatment instituted early is of importance not only in regard to preventing a possible immediate extension, but in preventing a possible catastrophe several years later.

Perhaps even more convincing than such alarming and perilous developments in occasional cases not treated sufficiently early, is the more frequent experience of finding evidence of instability in a lesion which, though originally innocent in appearance, had been given prompt treatment. Often this evidence is the gradual retrogression of the infiltration manifested by reduction in size of the roentgenogram shadow. Sometimes, however, it may be a positive sputum or gastric washing discovered only after many examinations. Stiehm<sup>10</sup> has called attention to the high proportion of early infiltrations of minimal extent which are associated with positive gastric washings if these are repeated sufficiently often. Finally, there may be progression despite sanatorium treatment. Such progressions or reactivations occurring in spite of treatment have in our experience always been of small extent and they are discouraging rather than immediately threatening in their consequences. On the basis of our experience with cases of this type we favor strict bed rest during at least the first two or three months of observation even of asymptomatic cases in young adults and our best results have been obtained in those instances in which we have been able to institute such a regimen. The general value of rest treatment, with or without associated collapse therapy, is so well established and has been so abundantly demonstrated as the fundamental means in combating tuberculosis that it scarcely requires reiteration. It is of interest, however, to note that in the past five years we have had but one case among those who have been diagnosed and placed under rest treatment in the minimal asymptomatic stage which has required pneumothorax, and this was for an excavation and local extension which were associated with an intercurrent acute respiratory infection within two weeks of the institution of bed rest. This was also the only minimal stage case which progressed while actually on a strict bed rest regimen. The pneumothorax in this case was successful in promptly arresting the disease.

#### INDICATIONS FOR TREATMENT

Since not all asymptomatic pulmonary tuberculosis discovered by routine roentgen-rays has such great potentialities for progression as was manifested in these case histories, the evaluation of pulmonary infiltrations and selection of cases for treatment is evidently a matter of difficulty and considerable clinical importance. A higher incidence of already stabilized lesions to be found with greater average age of population examined has been reported in all large scale case finding surveys. Our own experience, previously reported,<sup>2</sup> in which 38 per cent of a small group of untreated minimal asymptomatic cases progressed in an average follow-up period of two years, showed

that these progressions occurred mainly in the younger group. This led five years ago to the adoption of a policy of prompt treatment for all lesions of unknown stability and duration in persons under 30 years of age, regardless of the presence or absence of accompanying symptoms or laboratory signs of activity. In persons over 30, if the roentgenogram was not obviously that of an active process, the lesions have been observed closely but no treatment instituted unless it was known that they were of recent origin, or until there was symptomatic, roentgenographic or laboratory evidence of progression. This policy, though necessarily somewhat arbitrary, has been successful in that all of the active cases in the older group have been found to be so before they had progressed beyond the minimal stage and have not required a longer period of treatment than usual to become stabilized. In the younger group it is probable that a certain small proportion, certainly less than half, have been treated unnecessarily, but the risks of delay have been demonstrated to be excessive in the few cases in which there was failure to recognize the disease in its true incipency: Until some more reliable means are found than the laboratory methods now available for determination of potential activity an arbitrary selection on the basis of age is the only safe procedure. Contrary to the experience reported by Myers<sup>11</sup> that selection may be based on whether a demonstrable focus appears shortly after a first infection, as determined by a change in the tuberculin reaction, and may therefore be considered a benign primary focus, we have noted no lesser potentiality for progression of early infiltrative lesions in the originally negative as opposed to the originally positive reactors. Nor have we seen any lesions which resembled primary tuberculosis as seen typically in childhood, although we have now observed many medical and nursing students who have acquired positive tuberculin reactions between entrance and graduation. The vast majority develop no demonstrable lesions. In the few who have developed parenchymal foci these have been the typical subapical early infiltrates, without associated hilar lymph node enlargement, of the adult form of the disease.

The opportunity to observe a large number of asymptomatic cases of pulmonary tuberculosis exists in every institution of moderate size. The experience here recounted has comprised a total of over 100 cases of roentgenologically demonstrable lesions, all of them potentially serious and requiring clinical study and medical supervision or treatment. A majority of these cases has remained under observation sufficiently long so that the original evaluation could be checked by the subsequent clinical course. It is only such opportunity for continued study that allows one to appreciate fully the extreme danger of small recent infiltrations, especially in young persons. Factors other than age, such as race and the presence of diabetes mellitus, are also helpful in evaluating the probable future behavior of asymptomatic lesions. The character of the roentgenologic shadow in the case of minimal infiltrations, on the other hand, has proved an uncertain guide. These small

lesions, even when quite new, may possess a circumscribed or stringy appearance such as is frequently thought characteristic of old fibrotic processes. Reliance on such appearance, without further clinical study, including serial-roentgenologic observations for the detection of change is fraught with serious hazard. This is true in patients of any age period. It is only the conditions under which observation should be continued and the frequency of the examinations that may be guided by age. A single examination is not sufficient for accurate evaluation in patients of any age. At least six months of close observation are generally required before any case may be safely classified as arrested and the frequency of examinations relaxed to intervals of two or three months.

#### IV. REHABILITATION

A program of case finding and tuberculosis control is not complete without adequate consideration of the problems of rehabilitation. This is perhaps the most difficult aspect of the entire problem and has been, in our experience, the most disappointing in many respects. Similar to those of early diagnosis, the fundamental problems of rehabilitation are the responsibilities of the clinician. University hospitals as teaching institutions have a particular obligation to exercise leadership in this field. As employers they have the opportunity to do so by example. Their administrative officers need the coöperation and guidance of their clinical staffs both in respect to the supervision of individual cases and the formulation of general policies. The policy of this institution has not been to reject personnel, students or staff whose roentgenograms demonstrate pulmonary shadows and this, of course, accounts for the accumulation of so many cases of tuberculosis. Although the New York Hospital is not a rehabilitation center, no individual with tuberculosis has been kept from working or studying if the clinician decides that such disease is arrested. In those instances in which the disease appears to be recently arrested there is no rigid outline for rehabilitation. Each case is considered as an individual problem and we believe that such flexibility is necessary. Schedules in the medical and nursing schools and working hours in the hospital can often be organized to fit the individual need and adequate provisions for diurnal rest can be made available.

In table 3 is shown the number of persons in each of the professional groups whose disease was considered arrested at first examination, and the number in whom reactivation subsequently occurred. Of the total of 116 cases of tuberculosis in all the groups, 66 were originally thought to be arrested and 13 reactivations occurred in 11 of these. Six of this group had been accepted for part-time work following what was considered an adequate treatment period. The other seven, who had lesions which were arrested by all laboratory and clinical criteria, had begun work full-time. Two individuals following a period of rehabilitation broke down a second time and

treatment was necessary. All of the activations were of minimal extent, only one had symptoms and in none was a positive sputum found. The reactivations occurred in periods ranging from 6 to 48 months. In the group who were appointed for part-time work, the rehabilitation period was never less than four months, and the return to full-time activity in each had been gradual.

TABLE III

Status of Cases of Pulmonary Tuberculosis According to Activity in the Five-Year Period, July 1, 1939 to July 1, 1944

| Group                           | Total Cases<br>TBC | Number Considered<br>to Have Arrested<br>TBC on First<br>Examination | Number Who<br>Remained Arrested<br>Through Course | Total<br>Reactivations |
|---------------------------------|--------------------|----------------------------------------------------------------------|---------------------------------------------------|------------------------|
| Medical Students                | 7                  | 2                                                                    | 0                                                 | 2                      |
| Student Nurses                  | 10                 | 2                                                                    | 2                                                 | 0                      |
| Graduate Nurses                 | 68                 | 42                                                                   | 35                                                | 7                      |
| Post Graduate<br>Student Nurses | 15                 | 6                                                                    | 6                                                 | 0                      |
| House Staff                     | 16                 | 14                                                                   | 12                                                | 2                      |
| Total                           | 116                | 66                                                                   | 55                                                | 11                     |

In analyzing the rehabilitation failures no one reason common to all cases can be found. The reactivations occurred six months to 10 years after the first diagnosis of the disease and in no case had there been a sudden change in work, responsibility, or social status. In retrospect it is doubtful that any great change in the program that the individuals had undertaken under the clinician's guidance would have prevented their relapse. It should be emphasized that in all cases, the reactivations were minimal in extent, that in no case did the total extent of disease progress beyond the minimal stage, and that the ultimate prognosis for cure in each remains good. There were no deaths. In spite of the relatively high number of failures, the efficiency of the follow-up has prevented any disastrous result except in instances in which medical advice was not followed. Four individuals with active disease continued at work against advice. In three of these there was progression, one eventually requiring a thoracoplasty.

It is apparent that further measures are necessary to protect the arrested cases. Despite the not entirely satisfactory record, we continue to believe that complete rehabilitation is practical and possible in most cases. There is no evidence to indicate that the professional person with inactive tuberculosis endangers other hospital personnel or patients. In fact, it is probably safer for them to be in an institution where close clinical observation and guidance can be obtained, and should be expected, than in other situations where such safeguards are not or cannot be applied.

## V. EDUCATIONAL CONSIDERATIONS

The enormous value in terms of lives and years of invalidism which can be saved by systematic search, careful evaluation and adequate treatment of early tuberculosis is self-evident from even the relatively small clinical and statistical material that has been here presented. The utilization of such experience for first-hand instruction and demonstration is a most important aspect of any case-finding program conducted within a medical educational institution. There are, however, difficulties to be overcome and the more inclusive and efficient the program the more new educational problems are likely to arise. Perhaps first among these is the latent phobia which the name of the disease still tends to arouse. As more cases are discovered which might have gone unrecognized for years there is apt to grow an exaggerated idea of occupational hazards. The very measures taken to protect students and staff from danger of infection by patients with recognized disease may, if not carefully explained, lead to misconceptions concerning the epidemiology of tuberculosis. To overemphasize such measures as isolation technic or to fail to distinguish between the slight danger from an instructed and coöperative patient and the material risk in caring for a careless and uncoöperative one is poor teaching. A practicable technic which confers complete protection from all contact with the tubercle bacillus by those who are concerned with the care of patients has never been devised. The danger can and should be reduced but it cannot be eliminated. To exaggerate it in the minds of students or junior staff or to misplace the emphasis by setting up an invariable or over-elaborate routine is doing disservice both to their own education and to the care of the patients.

Another difficulty that we have found in attempting to use the experience of the case-finding program for teaching is in the presentation of the findings. The accomplishment, however important, is not dramatic and neither students nor a constantly changing house staff have the opportunity of personally following cases for the many years necessary to evaluate the efficacy of methods of prevention or treatment. This difficulty, in fact, applies to all phases of clinical teaching of tuberculosis. The proper selection of cases for treatment is more difficult in this disease as the fluctuation between progressive and retrogressive phases is more finely balanced than in most others. It is probably because of this balance between progression and healing that tuberculosis responds so conspicuously to rest and other non-specific measures in contrast to other infectious diseases. The enormously varied clinical picture may perhaps also be attributed to this unique and often unpredictable balance. Observation of a single case or even a dozen cases of tuberculosis may teach very little, may in fact be totally misleading so far as a thorough understanding of the clinical behavior of the disease is concerned. The material derived from a program of early case-finding must, therefore, be collected in the form of roentgenograms and case histories, and follow-up

data must also be available. A mere review of statistics cannot take the place of observation of individual cases in sufficient number.

Until a specific chemotherapy may become available for tuberculosis the great strides which can be made toward its control by early case-finding, accurate evaluation, and treatment by the methods now available should not be undervalued. Much can be achieved and the tools are available practically to eliminate tuberculosis as a cause of death or permanent disability, at least in any segment of the population which is so readily accessible for early diagnosis as are medical and nursing students and personnel. If a modern program of case-finding is introduced among them, and if they are made aware of the results and given the opportunity to contrast these with the advanced cases which still make up the majority to be found in the hospital wards and clinics, there will result a far reaching gain to medical education.

### SUMMARY

1. A continuous program for early tuberculosis case-finding among the medical students, undergraduate student nurses, post-graduate student nurses, staff nurses and medical house staff of a thousand-bed university hospital is described.

2. The cumulative incidence of pulmonary tuberculosis in these groups over a five year period was 2.8 per cent. Sixty-six, or 56.9 per cent of the 116 cases found were considered arrested at the time of first examination. The disease was minimal in extent at the time of diagnosis in 92.2 per cent of the cases.

3. The incidence of new cases annually was calculated to be 2.0, 5.2, and 6.0 per thousand per year among the medical students, student nurses, and graduate staff nurses, respectively. The data available were insufficient for the calculation of annual incidence rates among the postgraduate student nurses and the medical house staff.

4. The possible occupational hazards for students, nurses, physicians, and attendants are discussed and methods of control suggested.

5. The clinical evaluation of asymptomatic tuberculous pulmonary infiltrates is discussed and illustrative cases reported. Indications for treatment of patients with asymptomatic lesions of unknown stability are suggested on the basis of age selection.

6. An academic and professional rehabilitation program for students, nurses, and physicians with arrested pulmonary tuberculosis is reported. Among 66 such cases accepted for study or professional work reactivations occurred in 11. Such reactivations were detected in most before the appearance of symptoms, and the progressions were of small extent in all cases. Despite this relatively high incidence of reactivations the presence of arrested pulmonary tuberculosis is not regarded as a justifiable cause for rejection from professional careers.

7. The educational value, for undergraduate medical teaching and for graduate training, of an organized continuous tuberculosis case-finding program in every university hospital is discussed.

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## MORBIDITY AND MORTALITY IN SANTO TOMAS INTERNMENT CAMP \*

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THE internment of Americans and allied national civilians in the Philippine Islands for 37 months by the Japanese in Internment Camp No. 1 at Santo Tomas University, Manila, and two auxiliary camps, No. 2 at Los Banos and No. 3 at Baguio, was an experience unique in American history. A narrative account of the health, morbidity and mortality of the civilian internees is a story which is, on the one hand, a high tribute to the internees themselves and the medical care that they received, and, on the other hand, an indictment of their Japanese captors. These civilian internee camps are not to be confused with the more dreadful Prisoner of War Camps which were located at Cabanatuan, Camp O'Donnell, Fort Santiago and Bilibid Prison where American troops were imprisoned after their capture on Bataan and Corregidor.

This report is concerned chiefly with the Camp at Santo Tomas University, largest of the civilian camps, about which more information is available and through which the majority of the internees from the other camps were cleared before their repatriation. The writer served with one of the Army hospitals which was set up within this Camp after its liberation. Certain information concerning the two other similar camps is interspersed.

Some records of medical activities in the Santo Tomas Camp were made, but many were lost or destroyed in the confusion at the time of the liberation of the Camp. Fortunately, a few duplicate records and secret reports not available to the Japanese were kept, and it is from these sources that much of the present information was obtained. The records which remain intact have been deposited with the Recovered Personnel Section of the Army Headquarters. By compiling information gained from the official records and from information supplied by well-informed individuals, a reasonably accurate appraisal of the medical history of the Camp has been made. Dr. L. Z. Fletcher, Manila physician and former Chairman of the Medical Committee of Santo Tomas Camp, and other physicians furnished much essential information. Two former internees who are writing books on the Internment Camps generously provided material which will appear later in their books. Mr. F. H. Stevens' book will be entitled "Memories of Santo Tomas Internment Camp," and Mr. A. V. H. Hartendorp's book will be entitled "When the Flag Came Down." The records of the various Army hospitals which recovered many patients from these camps have been studied and statistically recorded. Some personal observations made on recovered personnel in Army hospitals are included. No medical records of the Camps at

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Los Banos and Baguio are known to exist, but a record of the deaths at the Baguio Camp was found and the names of the dead at Los Banos were taken from grave markers. Certain general information concerning these two camps was obtained by interviews with doctors who were interned therein, and the causes of the deaths in both camps were ascertained.

### THE CAMPS

The Japanese apparently had no plan for providing housing and food for the "enemy aliens" that they were to intern, and no thought had been given to their medical needs. By an agreement between the American Red Cross Emergency Committee, the Dominican Fathers of Santo Tomas University and the Japanese Military authorities, the walled campus of Santo Tomas University, consisting of about 50 acres and various university buildings, was selected as the site of internment. The first internees were admitted to the Camp on January 4, 1942. Americans and allied nationals were gathered from all the islands and gradually sent here.

The Camp population was not that of an "average" community. It was made up largely of well educated people of the executive and wealthy class. Many American women and children left the islands before the war started. Many young men were in the military service and, if they survived to be made prisoners of war, were separated from their families. An appreciable number of "old soldiers" from the Spanish-American War and the Philippine uprising were in the Camp. If they had Filipino wives and mestizo children, their families were not interned. British families from China were about evenly divided as regards sex. There was a disproportionately large number of men, especially old men. A maximum of 3,800 persons were interned at Santo Tomas. There were about 1,400 women and 700 children under the age of 17. In May 1943 an overflow of internees was sent to a new Camp at Los Banos, 50 miles south of Manila, the site of the College of Agriculture of the University of the Philippines. The first to go to Los Banos were the able bodied young men who were to work on farm projects. Later women and families were also sent to that Camp, and a "Holy City" of nuns, priests and Protestant missionaries grew up there. This Camp had a census of 2,146 persons in 1944. A third smaller Camp was maintained at Baguio in the Mountain Province where a census of 460 persons was reached. The Baguio internees were transferred to Bilibid Prison in Manila in December 1944. Census statistics of the three camps as of December 25, 1944 are shown in tables 1 and 2.

The internees at Santo Tomas were liberated in one of the grand and dramatic coups of the war on February 3, 1945 by an armored cavalry dash. The inmates of Bilibid Prison (including the internees formerly of Baguio) were freed on February 4 by the infantry and those at Los Banos by an even more spectacular combined paratroop and overwater operation on February 23. Filipino guerrillas contributed much to these operations.

TABLE I  
Census Statistics of the Three Camps

|                          | Manila<br>Camp 1 | Los Banos<br>Camp 2 | Baguio<br>Camp 3 | Total |
|--------------------------|------------------|---------------------|------------------|-------|
| Americans.....           | 2,870            | 1,589               | 394              | 4,763 |
| British, misc.....       | 745              | 329                 | 63               | 1,137 |
| British, Australian..... | 100              | 33                  | —                | 133   |
| British, Canadian.....   | 61               | 56                  | 9                | 126   |
| Netherlands.....         | 50               | 89                  | —                | 139   |
| Polish.....              | 25               | 22                  | —                | 47    |
| Norwegian.....           | 10               | 10                  | —                | 20    |
| Italian.....             | —                | 16                  | —                | 16    |
| French.....              | 7                | 1                   | —                | 8     |
| Spanish.....             | 2                | —                   | —                | 2     |
| Egyptian.....            | 2                | —                   | —                | 2     |
| German.....              | 1                | —                   | —                | 1     |
| Swiss.....               | 1                | —                   | —                | 1     |
| Slovak.....              | 1                | —                   | —                | 1     |
| Nicaraguan.....          | —                | 1                   | —                | 1     |
| Chinese.....             | —                | —                   | 1                | 1     |
| Mexican.....             | —                | —                   | 1                | 1     |
| Total                    | 3,785            | 2,146               | 460              | 6,399 |

TABLE II

Distribution of Internees at Santo Tomas According to Age Groups as of August 1944

|                  | Male | Female |
|------------------|------|--------|
| 0-15 years.....  | 355  | 332    |
| 15-17 years..... | 56   | 54     |
| 18-30 years..... | 350  | 402    |
| 40-50 years..... | 385  | 296    |
| 50-60 years..... | 320  | 215    |
| 60-plus.....     | 465  | 84     |

Santo Tomas University was an interesting and fairly satisfactory place for the internment of such a large number of people in spite of extreme overcrowding. Conversion of the University into a crowded internment camp presented acute administrative, as well as sanitary and health problems. The original administration of the Camp was under civilian Japanese authorities who permitted "supervised" self-government at the Camp through an "approved" Executive Committee and various sub-committees. This type of government was continued until the Camp administration was taken over by a Japanese military administration in February 1944. At that time drastic restrictions were imposed upon the Camp and practically all contact with the outside was prohibited.

During the first two years of internment, the internees were allowed to purchase with their own funds supplementary food and necessities which were brought to a market in the Camp. From July 1, 1942 to February 1944, a per diem for adults (children one-half) of from 35 cents to 75 cents (the per diem increased as inflation progressed) was allowed per individual by the Japanese and turned over to the Executive Committee for purchases for the common good such as foodstuff, medicines and surgical supplies.

This fund was augmented by very large sums from the American Red Cross through the Swedish Consul. There were many large private contributions to the fund. The monthly expenditure of the Executive Committee was about \$150,000.00. In 1942 a Japanese official in an address before the internees of Santo Tomas made the statement, "While we are victorious we can afford to be magnanimous." This was properly interpreted in the vice versa by the internees. After February 1944, the new regime discontinued the per diem allowance; food was provided by the Japanese "in kind," and purchases could no longer be made from outside except by the black market and by smuggling. In July 1944 the internees were forced to turn in all money except \$25.00 per person. Money could be deposited in the Japanese Bank of Taiwan (Formosa) or loaned (donated) to the Executive Committee. They were then allowed to withdraw \$25.00 per month per individual in Japanese occupation pesos. By that time inflation had taken place in foodstuff and Japanese occupation money had very little purchasing power.

#### MEDICAL ORGANIZATION AND EQUIPMENT

Immediately after the internees began to arrive at Santo Tomas, medical and sanitary needs were obviously urgent. No plans or suggestions were made by the Japanese. The doctors who were interned promptly formed themselves into committees and made plans for the health and sanitation of the Camp under the direction of Dr. C. N. Leach, a Rockefeller Foundation representative. Americans and Europeans who live in the tropics become keenly aware of the vigilance necessary in matters concerning health and sanitation, and good coöperation was given to the various committees by all internees.

Several medical clinics were started in the early days of the Camp and an improvised hospital was established. It soon became apparent that larger hospital facilities were necessary and the Executive Committee negotiated for the rental of Santa Catalina Convent adjacent to the University of Santo Tomas for a hospital. This hospital was equipped by donations and loans from Filipinos, Chinese, Swiss, Spanish and other nationals who were not interned, by various Philippine medical institutions and by purchases made through the funds of the Executive Committee. Several Manila hospitals and the Bureau of Health were most coöperative in providing facilities not available in the Camp hospital.

No great difficulties were encountered in the care of the sick in 1942 and 1943. Drastic changes in medical facilities were made in February 1944 after the Japanese physician in charge of the Medical Division War Prisoners' Camps issued orders that no physician except "enemy aliens" could practice in the Camp and caused to be closed to internees several civilian institutions where they had been hospitalized. All chronically ill and aged people who had been permitted to live in outside hospitals or domiciles were required to return to the confines of the Camp. Up to 1944,

patients requiring major surgery had been transferred to one of the Manila hospitals and usually operated upon by one of the Camp surgeons. Communicable diseases developing within the Camp had been promptly transferred to San Lazaro Isolation Hospital. It became necessary to provide means for major surgery and hospital care for all types of illness, including communicable diseases and the chronically disabled, within the Camp. Rapid expansion of the several annexes to the main hospital—one for children, one for contagious diseases, and several for the aged and chronic sufferers—was made. The Santa Catalina hospital had an average census of 100 to 120 patients daily in 1944; the Children's Hospital averaged 15 to 30; and the Tuberculosis and Isolation Section averaged 25 to 30. The various Convalescent Sections provided for an additional 300 patients.

Laboratory facilities were set up in the sections of the hospitals as they were established. Simple laboratory procedures on blood, urine, stools and sputum were carried out as needed. Parasitology technicians were available and were able to make diagnoses of malaria, amebic dysentery, and parasitism. There were insufficient or unsatisfactory media for bacteriological studies. Hence, cultural tests for bacillary dysentery or other bacterial diseases were not satisfactory. Serologic tests and more difficult examinations were occasionally sent to laboratories in Manila. In July 1944 the Japanese ordered that all laboratory specimens that could not be examined in the Camp be sent to a Japanese Army Laboratory. The physicians did not take advantage of that service.

Roentgen-ray facilities for internees were available during the first two years at the Philippine General Hospital and St. Luke's Hospital, but during the last year of internment, the physicians were dependent upon one poor fluoroscope in the Camp hospital.

Several of the doctors who were interned brought a supply of drugs from their own stocks or purchases at the time of internment. Dr. Leach made some purchases guaranteeing payment by the Rockefeller Foundation. Some drugs and medical supplies were bought from Manila stores in 1942 and 1943 by funds from the Executive Committee. Chinese merchants who owned most of the drug supply houses in Manila were very coöperative with the Camp. When almost all medical supplies were exhausted, a large shipment of American Red Cross medical supplies arrived on the Japanese repatriation ship, the "Teia Maru," in December 1943. Included in these were surgical supplies, blood plasma, vitamins, insulin, liver extract, anti-parasitic drugs, sedatives and anesthetics. There was suspicion regarding the equitable distribution of the Red Cross supplies but no actual proof that any were used by the Japanese or others. After this shipment was received, there was no means of obtaining additional supplies, except by requisitions submitted to the Japanese Military supply stores. During 1944 small quantities of quinine, emetine, sulfanilamide, vitamin B, calcium and glucose were supplied by the Japanese. Of the requisitions submitted to the Japanese for

medical supplies, it was estimated that 7 per cent were obtained after an interval of one to two months.

There was no medical historian in the Camp, and in spite of advice by physicians to the Executive Committee that better records of the medical activities and health of the community be kept and correlated, this was not done. A marvelous opportunity was missed to keep an up to date medical history of a closed and controlled white community living in the tropics. There was no physician on the Executive Committee, and final authority on technical and administrative matters pertaining to the health, morbidity and sanitation of the Camp was held by a layman.

#### PROFESSIONAL CARE

Medical care in the Santo Tomas Camp was provided by an average of seven active American physicians. Some doctors were repatriated in 1942 and in 1943, but they were replaced by others (U. S. Army medical officers) who were transferred into the Internment Camp from Prisoner of War Camps upon the solicitation of the internee committee to the Japanese. In the Camp there were two active dentists, one of whom was allowed to retain his own dental equipment. Sixty-six Army nurses from Bataan and Corregidor and 12 Navy nurses offered their services to the various medical facilities. A number of Red Cross personnel were active in the organization of the different medical services. Six Filipino Red Cross physicians and three Filipino nurses were employed regularly before the Japanese excluded them from the Camp in 1944. Volunteers among the internees provided the necessary male and female assistants and labor for maintaining the medical installations.

There was an average of five active physicians and one dentist at the Los Banos Camp and two physicians at the Baguio Camp. Medical needs were not as great in these two camps as they were in Santo Tomas. They did not have the large number of old persons and had few children. They were not greatly crowded and were able to grow more foodstuff. Medical and surgical supplies were acquired by these camps early in the period of establishment and they also received a share of the Red Cross supplies in December 1943.

#### SANITATION

The sanitation of Santo Tomas was a serious problem from the onset. There were only 100 toilet seats for 3,800 persons. The plumbing was of poor quality and frequently out of order. Water pressure was often too low to reach the upper stories of the buildings. The tract of land on which the University stands is only a few feet above sea level and ordinary pit latrines were not practical. Outside latrines were made by sinking oil drum barrels. Much of the area was completely inundated during the rainy or monsoon season.

Flies were a great menace to the Camp and no satisfactory means were at hand to control them. House flies and blue bottle flies were most numerous. They were suspected of transmitting amebic dysentery, enteric infections, and hepatitis. (The Army sprayed the area periodically with DDT from airplanes after Manila was liberated and the fly problem was immensely improved.)

Mosquitoes were ever present in enormous quantities during the internment period. Most of the mosquitoes were of the culicine pestiferous variety and were mostly night biters. The transmitter of dengue, the *Aedes aegypti* mosquito, was also present. There were probably no Anopheles mosquitoes in the immediate vicinity of the Camp. The *Anopheles minimus* is present in the suburbs and very prevalent in the neighboring foothills but does not seem to survive within the city of Manila.

Head lice and pubic lice were minor nuisances. There were no body lice. Fleas were present. Bedbugs were a major menace throughout the period of internment in spite of continuous drives to eradicate them.

Rodents, several kinds of rats and mice, were present in moderate numbers.

#### EPIDEMIOLOGY

Among the early activities of the Medical Committee was the inauguration of an inoculation program with the help of the Philippine Public Health Department. The entire Camp at Santo Tomas was inoculated against typhoid and paratyphoid fevers, cholera, dysentery (mixed) and smallpox. Inoculations were repeated in 1943 and 1944. In fact, the group inoculations were done twice in 1944; one time by the Public Health Department and again at the direction of the Japanese Medical Authorities. The response of the internees to the inoculation program was almost 100 per cent coöperation. Inoculation programs were also carried out in the Los Banos and Baguio Camps. The Japanese caused the entire Camp personnel to be inoculated with antiplague vaccine in 1944. There was thought to be an outbreak of plague in the Japanese Army in Hongkong about that time. An interesting problem arose. The internees refused to take the plague "shots" at first for fear they might be harmful, but six men volunteered to take the injections first, and after nothing happened to them, the others no longer hesitated.

The only epidemics that developed during the internment occurred in the summer of 1944. There were records of 223 cases of measles, 203 whooping cough and 116 cases of bacillary dysentery (type undetermined). The same three diseases became prevalent in Los Banos after some families were transferred from Santo Tomas to that Camp.

Upper respiratory infections were never a serious problem but did increase during the rainy season. Pneumonia was mostly confined to the aged, and most deaths attributed to this cause were in people over 60. Atypical or virus pneumonia was seldom diagnosed. Sinusitis and bronchial asthma

were occasionally seen. Ordinary allergic symptoms were infrequently encountered.

Streptococcal sore throat was a rare disease and scarlet fever did not exist in the Camp. A few patients developed rheumatic infection with fever, but genuine rheumatic fever probably was not seen. Mumps and chickenpox were occasionally seen.

Eight cases of poliomyelitis developed within the Camp with one death. Most of the cases developed in 1942 and caused great anxiety at the time.

About 14 cases of diphtheria occurred. Antitoxin was available for use in small quantity and all patients recovered. Treatment was limited to 6,000 units antitoxin per patient unless the condition was very severe. In two cases, severe post-diphtheritic paralysis developed.

Tuberculous patients were treated in sanatoria outside the Camp during the first two years. There was no more than the normal rate of new cases during the years 1942 and 1943. There was, however, a sharp increase during 1944. A survey of the juvenile population of the Camp was made with Mantoux tests in 1942. Four hundred twenty-six children, ages one to 15, were tested, and 18 per cent showed positive reactions. This type of survey was not repeated in 1943 or 1944. In spite of the high percentage of reactors on the early period of internment, there was never a high incidence of clinically active tuberculosis in young people. The older age groups were most susceptible to tuberculosis when they became undernourished. Fluoroscopic examinations were made on most of the personnel of the Camp in 1942. By that method, a total of 41 persons—28 males and 13 females—were found to have tuberculosis. Forty-three deaths among the internees in all camps were due to tuberculosis.

There were six cases of typhoid diagnosed at Santo Tomas with two deaths. It was not clearly ascertained if these individuals had been vaccinated. About 12 cases which were diagnosed paratyphoid fever occurred with no deaths.

In November 1944, a typhus scare occurred in the Camp. There were four or five patients whose symptoms were suspicious of the flea and rat borne typhus. Laboratory findings at first gave some confirmation to that diagnosis, but subsequent tests were inconclusive. This caused a drive against the rats to be carried out by the sanitary department.

Amebic dysentery was constantly one of the greatest threats to the health of the Camp. The only available actual statistics on new cases diagnosed covers the early months of 1942. Cases diagnosed by months are as follows: January, 2; February, 1; March, 1; April, 2; May, 3; June, 8; and July, 18. About 10 per cent of the Camp population was treated for this disease at some time. Emetine, carbarsone and yatren were available but the supply seldom was adequate for the demands. No case of liver abscess was diagnosed. There were two known deaths from amebic dysentery, and several other unqualified dysentery deaths may have been caused by amebae. Unfortunately, there were differences in opinion between some of the Camp



doctors and the laboratory personnel concerning the diagnosis of this disease.

The controversy over laboratory diagnoses was more serious and confusing in the field of bacillary dysentery. There was no one individual in charge of the various laboratories and no satisfactory method for the identification of pathogenic organisms. No system for getting a large volume of reliable bacteriological work done in the established Manila laboratories was worked out. Almost all of the inmates developed severe diarrhea at some time during their internment. Fortunately, the condition was usually mild and self limited. In a few individuals the disease was severe and 12 deaths were attributed to "dysentery." It was not known if the *Shigella dysenteriae* (Shiga) bacillus was involved in any of these cases but in ex-internee patients handled later by Army medical units only strains of the *Shigella paradyenteriae* organisms were found.

A very interesting situation arose out of a food handler examination report in July 1942. The report made in the Philippine Institute of Hygiene was as follows:

|                           |     |
|---------------------------|-----|
| Cases examined .....      | 155 |
| Amebae carriers .....     | 6   |
| Salmonella carriers ..... | 50  |

Upon receipt of that report, a Japanese medical officer appeared at the Camp to make an investigation. He ridiculed the medical personnel of the Camp for allowing such a condition to exist. He demanded stool examinations of every individual in the Camp within one week and promised the necessary equipment. He is reported to have said, sarcastically, "If you men from your 'super-American' medical institutions cannot clear up this situation, the Imperial Japanese Army doctors from third rate medical schools will do it." He is also said to have given a reprimand to the doctors for not studying the Japanese language and said, "Suppose the condition were reversed and you had thousands of Japanese to care for, how would you know their needs?" Actually there was neither an outbreak of dysentery nor clinical Salmonella type infections in the Camp at the time. The Japanese failed to send any equipment, failed to make a subsequent inquiry, and nothing came of the episode except the resignation of the first Chairman of the Medical Committee.

The symptom complex called "tropical sprue" was thought to exist in about 20 patients, most of whom had the condition before admission to the Camp. Some of these patients' symptoms were improved when liver extract injections were given regularly, but after food shortage occurred, their general course was downward and eight died.

Ascaris infestation was very prevalent among the children. Hookworm and trichiuris were more rare at Santo Tomas, but hookworm was frequent at Los Banos where the prevalence was blamed on Japanese soldiers and their habit of defecating ad lib about the Camp. No cases of schistosomiasis or paragonomiasis (flukes) were discovered. These parasites are present on the Island of Leyte. No trichiniasis was recognized.

No cases of malaria were known to have been contracted while in Santo Tomas Camp, but there were many patients who brought the disease to the Camp with them. The Camp at Baguio was not in a malarious district, but many inmates contracted malaria while in the Los Banos Camp. Two patients died at Santo Tomas and two died elsewhere from the cerebral type of this disease. The malaria cases were about equally divided between the vivax and falciparum types.

Dengue frequently occurred but was usually a mild disease. Many of the internees had had previous attacks. There were several dengue-like fevers to which no name was given. These fevers have long been known to Manila physicians, but clinical entities have never been sufficiently defined to justify distinctive names.

Hepatitis with jaundice was endemic but never reached epidemic proportions. About 5 per cent of the population developed hepatitis. Usually this disease was not severe but regularly caused moderate loss of weight and two deaths were attributed to it. One interesting observation was that after a new group of internees joined the Camp from the outside islands of Panay, Cebu, Mindanao, etc., an outbreak of jaundice would occur among them within a few weeks.

There were about 60 cases of acute gonorrhea under treatment in the early period of the Camp. The number of cases gradually diminished so that by 1944 this disease was rare in the Camp. A small clinic for the treatment of about 25 cases of syphilis was maintained throughout the period of internment. Only rarely was a new case discovered. Chancroid and lymphogranuloma venereum were also present in the Camp.

#### OTHER DISEASES

Actual records concerning non-communicable diseases that occurred in the Camp were very scarce and most of the information was obtained from interviews with physicians.

The following report of the Medical Committee for the period January to July 1942 was found.

A small number of individuals improved remarkably in health during the first year of internment. These were persons who were over-weight and who normally over-ate or over-drunk liquors. The Japanese strictly prohibited the use of liquor in the Camp and bootlegging was kept at a minimum. There were a few well known Manila "drunks" admitted to the Camp who became respected members of the community after a period of readjustment.

Gastric ulcer was not a frequent disease, but the patients suffering from this condition fared badly owing to lack of a satisfactory ulcer diet and two men died after hemorrhages. There were usually about 50 individuals on a special "ulcer diet."

Dr. E. E. Whitacre, one of the Camp physicians, in a survey of 1,042 women in the Camp who were in the age group for active menstrual cycles

in 1943, discovered that 125 had primary amenorrhea with sudden onset. Of this group, he found none in whom an organic cause could be ascertained and termed the cases "war amenorrhea." He attributed the condition to a neurogenic and hormonal imbalance caused by worry, fear, and anxiety. He extracted the urine of two women daily for five weeks and found the

TABLE III

Report of Diseases by Systems for the First Six Months of Internment  
(Actual Diagnosis Not Known)

|                                |     |
|--------------------------------|-----|
| Gastrointestinal.....          | 975 |
| Surgical.....                  | 515 |
| Respiratory.....               | 863 |
| Dermatological.....            | 493 |
| Cardiovascular.....            | 206 |
| Ear.....                       | 127 |
| Genito-urinary.....            | 110 |
| Eye.....                       | 89  |
| Gynecological.....             | 87  |
| Avitaminosis.....              | 85  |
| Arthritis.....                 | 73  |
| Neurological.....              | 60  |
| Acute infectious diseases..... | 46  |
| Hernia.....                    | 39  |
| Orthopedic.....                | 18  |
| Diabetes.....                  | 13  |
| Endocrines.....                | 6   |
| Psychoses.....                 | 6   |
| Paralysis.....                 | 5   |
| Malignancy.....                | 5   |
| Drug addiction.....            | 3   |
| Poisoning.....                 | 1   |

TABLE IV

Patients Sent to Outside Hospitals for Same Period

|                                           |     |
|-------------------------------------------|-----|
| Philippine General Hospital.....          | 223 |
| St. Luke's Hospital.....                  | 256 |
| San Lazaro Isolation Hospital.....        | 31  |
| Red Cross Hospitals (3).....              | 77  |
| Total.....                                | 637 |
| Patients sent outside for house care..... | 137 |

pituitary hormone to be present but found a total absence of the ovarian hormone. He believed these individuals should be treated with estrogenic substance but there were no hormonal preparations available. He found that most of these women resumed normal menstruation after several months of adjustment to their situation.

There were about 20 diabetics in the Camp. Insulin was often not available and a satisfactory diet was impossible. The severe diabetics naturally regressed rapidly and eight died.

Disease of the prostate was notably rare among a population in which there was a disproportionately large number of old men. Decrease in libido was said to have been a common experience in the Camp.

Fungus infections of the skin, impetigo, and eczematoid dermatitis oc-

curred frequently but did not become widespread problems. In a few instances the infection spread to a large area of the body and there were three or four cases of exfoliative dermatitis. Malaria, or prickly heat, troubled susceptible individuals rather continuously. Scabies was frequently seen. One interesting observation was the epidemic nature of herpes zoster. This condition occasionally attacked several individuals in groups at the same time.

The rate of mental disease was remarkably low. There were about 15 psychotics among the internees, but only six were known to have developed psychosis during the internment. Six of the psychotics were inmates of institutions at the onset of the war. The internees, apparently en masse, took a mentally defiant attitude toward their Japanese captors who daily made efforts to lower their morale and to cause humiliation. Psychoneuroses with somatic symptoms were either very infrequent or did not come often to the attention of the attending physicians, who were busy with organic diseases.

Misdemeanors and felonies were uncommon, the main offense being that of stealing food. Offenders were judged by an appointed committee of internees and punished by confinement or extra work.

Seventy-five babies were born during internment. There were two still births and three infant mortalities; but no maternal deaths. When a pregnancy occurred in the Camp, the Japanese authorities automatically imposed a 30-day jail confinement on the father. There were 15 babies born at the Los Banos Camp with no deaths.

Surgery was accomplished satisfactorily during 1942 and 1943 by use of well established Manila hospitals but equipment and supplies were not adequate in the Camp hospitals, which were used after February 1944. Catgut and other suture material, needles, bandages, adhesive tape and anesthetics became scarce, and at times necessary operations could not be performed. Gauze and bandages were washed and sterilized and used repeatedly. There was over-all about the normal expected number of general surgical and gynecological operations. There were about 100 appendectomies and about 10 cholecystectomies. A large number of tonsillectomies was done on children.

Perhaps the most interesting surgical condition encountered frequently was intestinal obstruction. This condition was encountered frequently in the malnourished. Many people were obstinately constipated, and as they lost their abdominal fat, the gut easily became obstructed. This occurred most often in individuals who had had previous abdominal operations and adhesions.

An inordinately large number of inmates developed inguinal hernia in 1944 after losing a large amount of weight. Hernias often developed suddenly on slight exertions. A few strangulated and required emergency operations. The great majority of hernias were not repaired, partially because the limited supply of surgical material prohibited optional operations.

Surgery within the Camp was accentuated by casualties from enemy shell fire after liberation by American forces. By this time United States Army Medical installations were present to lend assistance. Ninety-seven internees were wounded and 17 were killed by shell fire.

There were no facilities for performing autopsies within the Camp. A few autopsies were performed on patients who died in outside hospitals in the early part of the war.

ERA OF STARVATION

Prior to February 1944, individual food consumption had been limited, but in general, the available quantity was considered adequate for calories and fresh food. Food for the central kitchen was purchased by the Executive Committee which had adequate funds. Supplementary foods could be purchased by the internees with their own funds. A small individual issue of Red Cross foods from New Zealand, South Africa and Canada was received in 1942. It was thought that the original destination for these supplies was some part of the United Kingdom. In December 1943, after the arrival of the "Teia Maru," each individual received a 55 pound box of food from the American Red Cross. Some of the more frugal and far seeing saved most of this supply and credited it with prevention of death from starvation during the latter part of the following year.

When the Japanese began to supply rations "in kind," they promised a daily ration as follows: 400 grams rice, 100 grams fish, 20 grams sugar, and 10 grams cooking oil (coconut), which presumably was the daily ration for a Japanese soldier. Actually the promised quantity was never approached. The actual amount issued daily per individual is shown on table 5.

TABLE V  
Quantity of Food Issued Per Capita in 1944

| 1944              | Protein Grams | Carbohydrate Grams | Fat Grams | Calories |
|-------------------|---------------|--------------------|-----------|----------|
| February.....     | 36.6          | 295                | 13.8      | 1,452    |
| March.....        | 39            | 349                | 11.7      | 1,660    |
| April.....        | 35            | 289                | 9.8       | 1,380    |
| May.....          | 38.7          | 306                | 13.8      | 1,503    |
| June.....         | 39.1          | 355                | 17.8      | 1,736    |
| July.....         | 28.6          | 257                | 19.8      | 1,321    |
| August.....       | 29            | 285                | 11.5      | 1,360    |
| September.....    | 27.8          | 252                | 12.6      | 1,229    |
| October.....      | 24            | 203                | 12.4      | 1,020    |
| November.....     | 25.5          | 194                | 13.4      | 999      |
| December.....     | 19.6          | 185                | 9         | 898      |
| Average—1944..... | 31.2          | 270                | 13.2      | 1,323    |

This chart was completed only through December 1944. In January 1945, the allowance was further reduced and the total caloric supply per individual reached as low as 700 calories per day. Children under the age

of 11 years were allocated one-half ration by the Japanese, but they actually were issued a disproportionately large share of the daily ration.

There was no fruit after February 1944, but the Japanese occasionally allowed some vegetables. The vegetables were thought to be those discarded by the Japanese Military kitchens. The internees grew 117 tons of green vegetables within the Camp. About 75 tons of the rapid-growing Australian leafy vegetable talinum were grown. It had an estimated 60 calories per 100 grams and served as bulk in the diet. The tops of a yam-like vegetable called camote were used, and pigweed leaves were found to be edible.

In order to portray more vividly what it is like to eat the diet provided by the Japanese, I quote Mr. Hartendorp:

"During the last few months a typical breakfast consisted of a 'mush' made of 80 grams of rice or corn, or rice and corn, boiled in water with a little salt. It was measured out in a little dipper and usually served thin and watery. We were supposed to get only two meals a day but usually at noon a thin soup was served, about one cupful, made with rice, corn and greens from the garden. Toward the last, a soy bean mash or refuse which the Japanese began to send in daily from a mill was used to make soup. Supper, the main meal of the day, consisted of a 'stew' or if it was thinner than usual, a 'puree.' The staff fought hard to make this a 100 gram (raw) meal, but did not always succeed. This was also generally rice and corn; sometimes there was a substitution of camotes (a kind of sweet potato). If the camotes were served alone, there was generally a gravy (meatless) made of vegetables and some kind of spice. The rations were issued by the Japanese on a day to day basis and the staff never knew in advance what or how much they were going to get."

Some of the internees with sufficient hidden funds to pay the black market (in which Japanese guards participated) for foods and essentials were able to augment their diet. The prices of commodities in the black market as of December 24, 1944 is shown on the following table.

TABLE VI  
Black Market Prices

| Commodities                          | Equivalent in<br>U. S. \$ |
|--------------------------------------|---------------------------|
| Sugar, per kilo.....                 | \$105.00                  |
| Rice, per kilo.....                  | 60.00                     |
| Corned beef, per 12 oz. can.....     | 40.00                     |
| Evaporated milk, per 14 oz. can..... | 20.00                     |
| Margarine, per lb.....               | 90.00                     |
| Vegetable lard, per lb.....          | 90.00                     |
| Unrefined coconut oil, per qt.....   | 70.00                     |
| Smoking tobacco, per kilo.....       | 40.00                     |
| Cigarettes, per pack of 30.....      | 18.00                     |
| Charcoal, per kilo.....              | 10.00                     |

A medical survey of the internees was made in August 1944, partially to impress the Japanese authorities of the graveness of the disintegration taking place among the people. A part of that report is reproduced in the following table.

TABLE VII  
Medical Survey of August 1944

|                    | Ages 19 through 39 yrs. |    |     |   | Ages 40 to 60 yrs. |    |     |   | Over 60 yrs.  |     |     |    | Total      |    |     |   |
|--------------------|-------------------------|----|-----|---|--------------------|----|-----|---|---------------|-----|-----|----|------------|----|-----|---|
|                    | No. exams—1065          |    |     |   | No. exams—1153     |    |     |   | No. exams—516 |     |     |    | Exams—2734 |    |     |   |
|                    | *X                      | %  | *XX | % | *X                 | %  | *XX | % | *X            | %   | *XX | %  | *X         | %  | *XX | % |
| Urinary frequency  | 650                     | 61 | 24  | 2 | 855                | 74 | 42  | 3 | 360           | 70  | 83  | 16 | 1856       | 69 | 149 | 5 |
| Diarrhea           | 99                      | 9  | —   | — | 90                 | 8  | 1   | — | 38            | 7   | —   | —  | 227        | 81 | —   | — |
| Paresthesiae       | 205                     | 6  | 6   | — | 283                | 24 | 1   | — | 157           | 31  | —   | —  | 645        | 24 | 7   | — |
| Neuritic pains     | 175                     | 16 | —   | — | 258                | 22 | 3   | — | 126           | 24  | —   | —  | 559        | 20 | 4   | — |
| Ocular pain        | 210                     | 20 | —   | — | 211                | 22 | 3   | — | 98            | 19  | 4   | 4  | 569        | 21 | 3   | — |
| Failing vision     | 291                     | 27 | 2   | — | 571                | 50 | 6   | — | 244           | 48  | 41  | —  | 1106       | 41 | 12  | — |
| Emaciation         | 74                      | 7  | 2   | — | 212                | 18 | 11  | — | 242           | 48  | 73  | 8  | 528        | 20 | 56  | 2 |
| Edema—face         | 30                      | 2  | —   | — | 71                 | 6  | —   | — | 87            | 17  | —   | —  | 188        | 6  | —   | — |
| —ankle             | 119                     | 10 | —   | — | 324                | 28 | 10  | 1 | 268           | 53  | 27  | 5  | 711        | 26 | 37  | 1 |
| Skin—pellagra      | 5                       | —  | —   | — | 29                 | 25 | —   | — | 66            | 13  | —   | —  | 100        | 3  | —   | — |
| —infection         | 56                      | 5  | —   | — | 49                 | 4  | 1   | — | 9             | 1.7 | —   | —  | 114        | 4  | 11  | — |
| Mouth—lips cracked | 82                      | 7  | —   | — | 200                | 17 | 2   | — | 176           | 35  | 1   | —  | 458        | 17 | 3   | — |
| —tongue sore       | 182                     | 17 | 4   | — | 287                | 24 | 3   | — | 216           | 43  | 8   | —  | 685        | 25 | 15  | — |
| Pallor             | 300                     | 27 | 11  | 1 | 453                | 40 | 11  | 1 | 259           | 50  | 29  | 5  | 1012       | 37 | 51  | 2 |

\* X—Moderate    \* XX—Severe

A large number of internees was weighed in August 1944 and these figures are compared with those given in official records at the time of internment.

TABLE VIII  
Weight of Internees in August 1944 Compared with January 1942

|             | Number | Average Weight<br>Jan. 1942 | Average Weight<br>Aug. 1944 | Average Pounds<br>Lost |
|-------------|--------|-----------------------------|-----------------------------|------------------------|
| Male.....   | 1,557  | 171                         | 140                         | 31                     |
| Female..... | 1,203  | 132                         | 114                         | 18                     |

Another similar survey was made in January 1945 and revealed very astounding figures regarding weight loss. The following figures are even more significant when it is realized that about 80 per cent of the personnel surveyed had varying degrees of nutritional edema which accounted for a part of the body weight.

TABLE IX  
Weight of Internees in January 1945 Compared with January 1942

|             | Number | Average Weight<br>Jan. 1942 | Average Weight<br>Jan. 1945 | Average Pounds<br>Lost |
|-------------|--------|-----------------------------|-----------------------------|------------------------|
| Male.....   | 1,506  | 172                         | 121                         | 51                     |
| Female..... | 1,232  | 132                         | 100                         | 32                     |
| Total.....  | 2,738  | 154                         | 112                         | 42                     |

Nutritional edema, popularly known as wet beri-beri, gradually became prevalent, so that by December 1944 about 75 to 90 per cent of the adult population developed various degrees of edema. Constipation or loose stools and polyuria and nocturia accompanied the edema. Neuritic symptoms or signs in the extremities occurred in about 20 per cent of the internees. Some had pains in the legs, others had paresthesiae and three or four patients developed foot drop. The deep reflexes were occasionally lost. Some individuals complained of numbness in their fingers causing discomfort in common duties and playing cards. A supply of thiamine chloride was usually available but generous doses of this drug had little or no influence on the edema, and cases with actual neuritic signs responded to it poorly. A regular issue of thiamine was made after the arrival of Red Cross supplies in December 1943, but a few "old timers" who refused to take any such new-fangled drugs were said to fare no worse than the others who took vitamins regularly.

Signs of vitamin A deficiencies such as dryness and roughness of the skin, perioral fissuring, were observed frequently. Night blindness occasionally developed, but a more frequent complaint was a general dimness of vision. Others complained of blind spots. Most of these visual disturbances and skin changes cleared up when adequate food was provided.



Early pellagrous changes in the skin and redness or soreness of the tongue were not rare. Signs of riboflavin deficiency such as cheilosis were frequently seen. Scurvy was apparently non-existent, although some patients developed sore gums that bled easily and were thought to be improved by the use of ascorbic acid.

Anemia of some degree existed in almost all of the internees by the end of 1944. The usual finding was about 3,500,000 red cells with 60 per cent hemoglobin. Many individuals purchased iron and liver extract from Manila drug sources as long as contact could be made and funds were available. The Camp supply of iron and liver was reserved for individuals whose red blood count was below three million. One interesting observation was that the blood count rose in the late stages of severe malnutrition; probably due to hemoconcentration.

The mortality from malnutrition rapidly increased in December 1944. The Japanese authorities issued orders that this diagnosis would no longer be used on death certificates and demanded that eight death certificates be changed. One of the Camp physicians was jailed after he refused to comply with those orders.

An occasional internee was executed by the Japanese during the three years. As the military situation grew worse for the Japanese in January 1945, they became more desperate and on one occasion executed four Camp Committeemen, including the Chairman of the Executive Committee.

#### AFTER LIBERATION

After the internees were liberated on February 3, 1945, they were given no rest. The Japanese who remained strongly entrenched in the old Spanish walled city "Intramuros" placed Santo Tomas Camp and its adjacent Santa Catalina Hospital under fire for five days from February 7 to February 12. When the shelling started, about 200 patients from the various sections of the hospital were transferred to U. S. Army medical installations which were being set up nearby. One U. S. Army Clearing Company (363rd) began operating a hospital within the Santo Tomas Camp on February 4. It provided care for a maximum of about 400 patients while the institution was under fire and received a unit citation for meritorious service. The Fifth Field Hospital supplanted the Clearing Company on February 24, and this hospital, in turn, was relieved by The 120th General Hospital on April 12. The Santa Catalina Hospital and the auxiliary units ceased to function as soon as the first Army hospital was established.

The sick and debilitated internees liberated at Los Banos were first cared for by an Army Clearing Company located at Muntinlupa, 40 miles south of Manila, then rather deep in enemy territory. An Army Evacuation Hospital soon took over their care at that site. As soon as road blocks were opened, transfer of these patients to Santo Tomas was started.

Santo Tomas Camp became the "clearing house" for all repatriation, and the Army hospital situated within the Camp became the site for processing

and evacuation of all ex-internees requiring hospitalization. Hospital accommodations on hospital ships or on troop ships with hospital facilities were arranged for patients who requested repatriation to the United States or Australia. Repatriation of ex-internees was started by air evacuation on February 12, while fighting continued in the City of Manila. As soon as Manila harbor was opened for shipping, water evacuations were started. By June 15, 5,257 individuals had been repatriated, including 344 hospital patients.

There was frequent transfer of patients between the various Army hospitals, and the former inmates of Baguio, Los Banos and Santo Tomas became mixed. A composite of the diagnoses made in six Army hospitals on all former internees is shown in the following table.

In addition to the patients treated in the various Army hospitals, many were treated as out-patients in the dispensaries operated by the hospitals. The dispensary of the hospital at Santo Tomas received from 100 to 300 out patient visits daily from internees, or an average of 3,000 visits monthly from February to June 1945. All cases of mild malnutrition were treated there, and enormous quantities of vitamin preparations and symptomatic remedies were dispensed. In the dispensary it was discovered that 80 per cent of the internees whose stools were examined were infested with ascaris. The incidence of amebiasis was found to be 18 per cent, and that of hookworm 8 per cent in the stools which were examined. A few infestations with *Giardia lamblia*, trichiuris and strongyloides were found. Head lice and pubic lice were frequently seen in the dispensary, but no body lice were found.

A surprising finding in the dispensary was the near absence of psychoneurotic symptoms among the internees. This was considered remarkable when most of the patients were malnourished, had unpleasant memories of three years imprisonment, and many had lost one or more members of their families during that period.

The findings made in the Army hospitals confirmed those made by the internee medical staff on the status of malnutrition. A considerable number of patients continued to die during the first month in the Army hospitals. The crescendo of disintegration due to prolonged starvation was at the apex at the time of liberation. Usually starvation and the formation of nutritional edema was a readily reversible process. When adequate plasma infusions were given, a satisfactory diet resumed and proper rest achieved, the edema cleared promptly and strength was rapidly recovered. In a few individuals, however, the process was no longer reversible and it was not possible to build the blood plasma protein level up to normal. There were 25 such patients treated in Army hospitals who were unable to tolerate a satisfactory diet, failed to gain in strength and weight, and after continuing a downward course, died. All gradations between the two extremes were seen.

Edema varied from pitting of the feet to gross edema involving the entire body with anasarca. We believed that the popular term "wet beri-beri" was not applicable to most cases. Less than 10 per cent were found to

TABLE X  
Diagnoses Made on Ex-Internees in Army Hospitals

|                                  |      |
|----------------------------------|------|
| Malnutrition.....                | 567  |
| Tuberculosis.....                | 76   |
| Traumatic wounds.....            | 63   |
| Gastroenteritis.....             | 51   |
| Malaria.....                     | 43   |
| Respiratory infections.....      | 41   |
| Hepatitis.....                   | 37   |
| Heart disease.....               | 37   |
| Diarrhea.....                    | 34   |
| Dysentery (unqualified).....     | 33   |
| Fever (undetermined origin)..... | 22   |
| Pneumonia.....                   | 21   |
| Dengue.....                      | 20   |
| Psychoses.....                   | 17   |
| Dermatitis.....                  | 16   |
| Pregnancy.....                   | 13   |
| Minor surgery.....               | 11   |
| Carcinoma.....                   | 10   |
| Asthma.....                      | 9    |
| Arthritis.....                   | 9    |
| Scabies.....                     | 7    |
| Hernia.....                      | 6    |
| Senility.....                    | 6    |
| Diabetes.....                    | 5    |
| Paratyphoid fever.....           | 4    |
| Heat exhaustion.....             | 3    |
| Neuritis.....                    | 3    |
| Syphilis.....                    | 3    |
| Lung abscess.....                | 3    |
| Cholecystitis.....               | 3    |
| Abscesses.....                   | 2    |
| Pleurisy.....                    | 2    |
| Pyelitis.....                    | 2    |
| Sprue.....                       | 2    |
| Cirrhosis of liver.....          | 2    |
| Blood dyscrasia.....             | 2    |
| Anemia.....                      | 2    |
| Phlebitis.....                   | 2    |
| Goiter.....                      | 2    |
| Appendicitis.....                | 1    |
| Rheumatic fever.....             | 1    |
| Typhoid fever.....               | 1    |
| Fibrositis.....                  | 1    |
| Prostatic hypertrophy.....       | 1    |
| Epilepsy.....                    | 1    |
| Poliomyelitis acute.....         | 1    |
| Brain tumor.....                 | 1    |
| Peptic ulcer.....                | 1    |
| Cellulitis.....                  | 1    |
| Herpes zoster.....               | 1    |
| Total.....                       | 1202 |

have sufficient nerve changes to warrant the diagnosis of beriberi. The edema was found to be due to hypoproteinemia. Blood plasma protein determinations were low in all cases. Some were found to be as low as 4.2 grams per 100 c.c. In others the total protein values appeared only slightly below normal, but when the albumin and globulin fractions were determined, it was found that the albumin fraction was disproportionately low, and in a few instances, there was reversal of the albumin-globulin ratio. It was not possible to determine the critical level of plasma protein at which edema

could be expected to develop. Precipitation of edema was apparently dependent upon secondary factors such as the A-G ratio, the salt and water intake, the amount of exercise taken, fever, and in a few instances upon concurrent kidney, liver, or heart disease.

In general, the children remained fairly well nourished, but about 10 per cent of them also had nutritional edema. The majority of children ate well and gained strength rapidly after liberation. About 25 per cent of them apparently did not have full tolerance for fats, and after eating butter or chocolate, developed diarrhea and abdominal distention. In a few instances, the abdominal distention persisted more than 30 days and simulated celiac disease. No frank rickets was seen, and we found no evidence that bony growth of the children had been retarded.

Many of the early diagnoses made in the Army hospitals were clinical opinions which were not always confirmed by laboratory findings. This was particularly true in the field of enteric infections. The terms dysentery, diarrhea, and gastroenteritis were used frequently and without uniformity in interpretation. Adequate laboratory procedures for the detection of pathogenic organisms in the stools were not frequently carried out during the first month after the liberation.

After April 12, an effort was made to study the diarrhea and dysentery problem. Routine proctoscopic examinations and repeated stool cultures were made on all hospital patients with diarrhea or with symptoms suggestive of enteric infection. By the time this service was organized, the majority of the sick internees had been repatriated. The series of patients thoroughly studied is small but is probably indicative of the findings that would have been made if all patients had been so examined. We were able to demonstrate *Endameba histolytica* trophozoites in 11 patients and histolytica cysts in six others by proctoscopic examinations made on 36 internees. *Shigella paradysenteriae flexner* was cultured from one patient of this group, and another patient had a positive blood agglutination for paratyphoid A in 1:640 dilution, although the bacilli were not recovered from the stool. The diagnosis of bacillary dysentery was made on characteristic proctoscopic findings of acute catarrhal inflammation of the rectum and sigmoid in four patients with negative cultures. Proctoscopic examination was the method of choice in the diagnosis of bacillary dysentery, whereas the cultural findings were often disappointingly negative. On the other hand, proctoscopic findings were frequently indefinite in amebic dysentery even when trophozoites were numerous. In only three patients in this small group were the characteristic amebic ulcerations seen.

A few patients did not wish repatriation and remained in the hospital a sufficient period of time so that more detailed studies could be made on the effects of prolonged malnutrition. There were also a few "escapees" who were late arrivals at the Camp and a small number left behind at Baguio who arrived at Santo Tomas after Baguio was liberated in May. Better labora-

tory facilities were available to study the late arrivals. The following five cases are illustrative of the variety of clinical states seen and each may be said to represent a group.

*Class 1: Malnutrition, mild.* In this group there was often a mild degree of nutritional edema in addition to moderate weight loss. This type of patient did not require hospitalization and responded quickly to ample diet. Many patients of this group developed diarrhea and occasionally some abdominal distention after the sudden change to an ample diet. The speed of recovery in the mildly malnourished was more or less in inverse ratio to the age of the individual. Example, a 55 year old American business man who had spent the entire three years in Santo Tomas had lost 60 pounds, down to 119. He had edema up to the knees, was easily fatigued, had nocturia two times nightly, but no other symptoms. He was able to eat the regular diet in the main Camp kitchen after liberation, and was given vitamin capsules in the dispensary. He had loose stools for three days, but his digestion remained good and the edema subsided within five days. He gained 15 pounds in weight within the next 20 days. His strength returned rapidly and he felt perfectly well.

*Class 2: Malnutrition, moderate.* British housewife, age 42. The past three years had been spent in internment, a part of the time at Baguio. At the time of admission to the hospital, there was edema of both lower extremities and some pitting of the sacrum and lower abdomen. She was very easily exhausted and had three or four loose stools daily. Her weight was 98 pounds after losing 36 pounds. There were no specific signs of vitamin deficiency. The red blood cell count was 3.6 million, hemoglobin 60 per cent. Total plasma protein on admission was 5.8; albumin 3.0; globulin 2.8 per cent; and after seven days' treatment, the total protein was 7.1, with albumin 4.6 and globulin 2.5 per cent. Other laboratory findings were essentially negative; no pathogenic organisms were found in the stool. She was placed on a high protein and high vitamin diet with multivitamin capsules, and was given two units of blood plasma daily for three days. By the fourth day she had an excellent appetite; the peripheral edema had almost entirely disappeared. Weight and strength were gained rapidly, and she was discharged on the twelfth hospital day.

*Class 3: Malnutrition, moderate with dysentery.* Recovery of these patients was dependent on the subsidence of the severe diarrhea. In some cases pathogens were not found after thorough search, but *Endameba histolytica* cysts or trophozoites were found frequently in the well studied cases. Example, a Belgian nun was admitted with massive edema of lower extremities, and with a history of 12 to 15 stools daily for past six weeks. She was able to tolerate a light diet. Two units of plasma, with other supportive treatment, were given daily for six days without improvement. At that time proctoscopic examination revealed ragged linear ulcerations in the upper rectum and trophozoites of *Endameba histolytica* were demonstrated.

Treatment was started with emetin and diiodoquin. The diarrhea subsided within four days. She began to eat a regular diet and eight days after starting the chemotherapy no edema was present.

*Class 4: Malnutrition, severe.* Cases of this type usually presented specific signs of vitamin deficiency in addition to the protein deficiency and great loss of weight. There were profound disturbances of physiologic functions; recovery was slow, and in some instances, probably never complete. Example, a 65 year old man was admitted with massive edema of lower extremities and scrotum, and some edema of the face. His tongue was red and sore. There was marked periorbital fissuring with cheilosis. The skin was pale, rough and dry on the extensor surfaces of the extremities with numbness and objective hypesthesia. He had marked frequency of urination and nocturia. He complained of dimness of vision. Laboratory findings: red blood count 2.9 million with 45 per cent hemoglobin; urinalysis negative, except maximum concentration was 1.020 after dehydration. *Endameba histolytica* cysts were demonstrated in the stools. Total plasma protein four days after admission was 6.2, with albumin 2.5 and globulin 3.7 per cent. He was treated with general diet, liver extract, two units blood plasma daily, and with oral diiodoquin for the amebiasis. Improvement was slow, but after 12 days most of the edema had subsided. At that time the plasma protein was 7.0; albumin was 3.8; and globulin was 3.2 per cent. Daily plasma infusions were discontinued and after five days the edema recurred and increased during the next five days. The plasma protein dropped to 6.3, the albumin to 1.3 and the globulin to 5.0 per cent. Daily infusions with two units of plasma were resumed and the protein fraction of the diet increased. The edema again subsided after eight days. The plasma protein rose to 7.1, the albumin to 3.8 and the globulin to 3.3 per cent. After 60 days of hospitalization, he continued to be very weak and had a poor appetite. The diarrhea had subsided but he was unable to gain weight satisfactorily. It is doubtful if this man will make a complete recovery.

*Class 5: Malnutrition, severe, with irreversible changes.* It was this type of patient which accounted for the high mortality rate among the internees during February after their liberation. Many older people were unable to respond to adequate treatment and succumbed. Example, a 75 year old man was admitted on litter, unable to walk. He had lost about 65 pounds weight, down to 104 pounds. He was incontinent of urine and feces. There were frequent diarrheal stools. He was delirious part of the time. There was neither fever nor evidence of acute infection. Red blood cell count was 3.2 million; white blood cell count 7,800. Blood plasma protein was 5.0, with albumin 2.7 and globulin 2.3 per cent. Urinalysis negative. No pathogenic organisms recovered from the stool. Treatment consisted of whole blood and plasma infusions, liver extract, thiamine, niacin and other supportive and symptomatic measures. He failed to show any improvement, gradually became weaker, and died 14 days after admission.

## DEATHS

There was a total of 435 known deaths among the American and Allied Nationals from January 4, 1942 to June 4, 1945. Many of the deaths in 1942 and 1943 occurred in domiciles or civilian hospitals. Records of as much information as could be obtained concerning all deaths were carefully kept. The vast majority of deaths occurred among the Santo Tomas group, not only because it was the largest Camp, but also because the chronically ill,

TABLE XI

Known Causes of Deaths among American and Allied National Civilians from  
January 4, 1942 to June 4, 1945

|                                      |     |
|--------------------------------------|-----|
| Heart diseases.....                  | 82  |
| Malnutrition and "beri-beri".....    | 60  |
| Tuberculosis (all forms).....        | 43  |
| Cancer (all types).....              | 31  |
| Pneumonia (all types).....           | 26  |
| Enemy shell fire.....                | 19  |
| Dysentery (unqualified).....         | 12  |
| Senility.....                        | 11  |
| Cerebral hemorrhage.....             | 9   |
| Executed by enemy.....               | 9   |
| Sprue (?).....                       | 8   |
| Accidents.....                       | 8   |
| Intestinal obstruction.....          | 7   |
| Nephritis.....                       | 7   |
| Cirrhosis of the liver.....          | 4   |
| Anemia.....                          | 4   |
| Malaria.....                         | 4   |
| Diabetes.....                        | 4   |
| Gastric ulcer.....                   | 4   |
| Stillborn.....                       | 3   |
| Septicemia.....                      | 3   |
| Psychosis.....                       | 3   |
| Appendicitis.....                    | 3   |
| Hernia strangulated.....             | 3   |
| Intestinal hemorrhage.....           | 3   |
| Lung tumor.....                      | 2   |
| Brain tumor.....                     | 2   |
| Peritonitis.....                     | 2   |
| Hepatitis.....                       | 2   |
| Encephalitis.....                    | 2   |
| Pernicious anemia.....               | 2   |
| Meningitis.....                      | 2   |
| Cholecystitis.....                   | 2   |
| Typhoid fever.....                   | 2   |
| Dysentery (amebic).....              | 2   |
| Suicide.....                         | 2   |
| Bombing by enemy (1942).....         | 2   |
| Rheumatic infections.....            | 2   |
| Paresis.....                         | 1   |
| Epilepsy.....                        | 1   |
| Lung abscess.....                    | 1   |
| Bronchiectasis.....                  | 1   |
| Homicide (by another internee).....  | 1   |
| Homicide (by Japanese beating).....  | 1   |
| Congenital disease of the spine..... | 1   |
| Pancreatitis.....                    | 1   |
| Prostatic hypertrophy.....           | 1   |
| Poliomyelitis.....                   | 29  |
| Cause unknown.....                   | 435 |
| Total.....                           | 435 |

the aged, and debilitated were retained there. There were only 20 deaths in the Baguio Camp and 21 deaths at Los Banos. The following table of the causes of deaths has been compiled by adding information obtained from many sources to the secret list obtained from Mr. C. A. Grant, the Custodian of Property of the Deceased. This list includes deaths at all camps and is thought to be complete, excluding the possibility that there were a few American escapees who died in remote parts of the islands while hiding from the Japanese.

TABLE XII  
Age Distribution of Deaths among the Internees

| Age               | Male      | Female   |
|-------------------|-----------|----------|
| 0-1 .....         | 4         | 7        |
| 1-10 .....        | 2         | 1        |
| 10-20 .....       | 2         | 2        |
| 20-30 .....       | 11        | 2        |
| 30-40 .....       | 12        | 9        |
| 40-50 .....       | 20        | 9        |
| 50-60 .....       | 55        | 5        |
| 60-70 .....       | 134       | 10       |
| 70-80 .....       | 89        | 6        |
| 80-90 .....       | 5         | 3        |
| 90- .....         | 1         | 0        |
| Age unknown ..... | 40        | 6        |
|                   | <hr/> 375 | <hr/> 60 |

## DISCUSSION

The statistics on causes of death presented here are probably not entirely reliable. During the first two years of internment most deaths occurred outside the Camp in civilian institutions, often under the care of civilian physicians. Some of the diseases to which deaths were accredited were taken from death certificates; others were merely "hearsay" diagnoses. In 1944 and 1945, duress from the Japanese probably influenced the diagnoses that were recorded on death certificates.

As may be seen by the table of causes of death, heart disease led the list. Some of these deaths were due to coronary disease, valvular hypertension disease, but in others the heart condition was probably only a terminal state. Pneumonia ranked high in the list, but this disease was also often a terminal condition. Senility was recorded on some certificates. This is not a very satisfactory diagnosis. Sprue was listed as causing eight deaths, but it is doubtful if that diagnosis was justified in all cases. The deaths attributed to unqualified dysentery are an enigma. Adequate laboratory work was not done on most cases and autopsies were not performed. Judging from our findings on recovered personnel, we would wager that many of the cases of sprue and unqualified dysentery were actually amebic dysentery.

It is of interest to compare the causes of death among the internees with the 15 leading causes of death in the total Christian population of the Philippines as reported by the Bureau of Health for the year 1937.

It is difficult to compare the ratio of the various causes of death in the



TABLE XIII

### Known Deaths from All Causes—All Camps—By Months

[illegible]

The crude death rate in the Philippines in 1937 was 20.97 per 1,000 Christian population. The crude death rate among the internees was 16 per 1,000 in 1942; 13.2 per 1,000 in 1943; 19.2 per 1,000 in 1944; and at the rate of 72.4 per 1,000 during the first three months of 1945. For the purpose of further comparison it may be stated that the crude death rate for the total population of the United States for 1942 was 10.4 per 1,000.

TABLE XIV  
Leading Causes of Death in the Philippines in 1937

|                             | Ratio to Total |
|-----------------------------|----------------|
| Tuberculosis.....           | 13.14          |
| Bronchitis.....             | 10.53          |
| Bronchopneumonia.....       | 9.69           |
| Senility.....               | 9.48           |
| Congenital debilities.....  | 7.86           |
| Beri-beri.....              | 6.59           |
| Diarrhea and enteritis..... | 4.59           |
| Influenza.....              | 3.81           |
| Malaria.....                | 3.75           |
| Pneumonia.....              | 3.15           |
| Violent deaths.....         | 1.54           |
| Dysenteries.....            | 1.42           |
| Puerperal states.....       | 1.27           |
| Heart disease.....          | 1.25           |
| Meningitis.....             | .94            |

### CONCLUSIONS

1. The health of the 3,800 American and Allied National Civilian internees who were incarcerated in the Internment Camp at Santo Tomas University, Manila, P. I. and the 2,600 other civilian internees in the Philippines was not deleteriously influenced during 1942 and 1943, the first two years of imprisonment. The crude death rate was less than that of the Philippine civilians and not notably greater than that of an ordinary American community. During that period there were no epidemics within the camps and the sickness rate was never high. The internees received good medical care from their own physicians and were thoroughly coöperative in all matters concerning health and sanitation.

2. The health of the internees seriously deteriorated in 1944 and 1945 during an era of forced gradual starvation imposed by their Japanese captors. Sixty persons died directly from malnutrition. In many others, malnutrition was a contributory cause to death.

3. A total of 435 known deaths occurred among the American and Allied National Civilians from January 4, 1942 to June 4, 1945 in the Philippines. Records of the causes of deaths were compiled and are published herewith.

4. Information concerning the epidemiology and morbidity in the camps during captivity was obtained from various sources and has been presented.

5. United States Army medical installations recovered many patients from the internment camps. Interesting observations made by these units are also reported herewith.

6. Some personal observations made on ex-internees suffering from malnutrition and dysenteries are recorded. From our findings, we believe that the majority of the internees who were hurriedly repatriated to the United States and to other countries harbored pathogenic organisms in the intestinal tract such as *Endameba histolytica* dysentery bacilli and round worms. These possibilities should be kept in mind by civilian physicians who are called to treat these people.

# SURVEY OF DYSENTERY IN PRISONERS OF WAR\*

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It is inevitable that during wars outbreaks of diarrheal diseases should become a major medical and sanitary problem particularly in combat areas. By far the most important single agent in the production of ineffectiveness due to diarrhea is the group of bacillary dysentery organisms of the genus *Shigella*. Evidence points to the fact that these organisms are transmitted by direct or indirect person-to-person contact.<sup>1, 2</sup> Consequently, the most important preventive measure to be taken in order to control dysentery is a thorough stool survey of all food handlers.

In view of the fact that prisoners of war (POW) are frequently assigned to assist in army messes and to work in hospital wards, it is obvious that they may become a possible source of contamination. It is, therefore, essential to examine their stools for intestinal pathogens, both bacillary and parasitic, before assigning them to such work. During the course of such routine examinations in our laboratory, 4 of the first 10 stool specimens submitted were found to be positive for *Shigella paradysenteriae* of one type or another. This stimulated our interest in this problem, and it was decided to make routine stool examinations on an entire labor battalion of POWs in the European Theater of Operations. The survey eventually included a total of 264 German POWs; 214 were examined in December and 50 in February. In both groups there was considerable active dysentery upon arrival, although the incidence of acute diarrhea was lower in the February group.

The objects of this study were as follows: To determine the overall incidence of *Shigella* organisms in the entire group of 264 POWs; to determine which of the positive cases had actually had diarrheal symptoms within a reasonable length of time; to determine the incidence of chronic carriers; and, finally, to ascertain the incidence of associated parasites. Observations were also made as to symptomatology, character of stools, and effectiveness of sulfonamides in the treatment of bacillary dysentery.

## LABORATORY PROCEDURES

Fresh stool specimens were submitted to the laboratory in ordinary paper sputum cups. Cultures were made immediately on S. S. agar or desoxycholate-citrate agar plates. The following day suspicious colonies were selected and transferred to Kligler's slopes. Cultures showing typical acid butt and alkaline slope on this media were immediately checked by a spot plate agglutination test using a strong polyvalent Flexner antiserum. This

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serum was prepared in the following manner: A polyvalent antigen was made by pooling 18-hour broth cultures of Flexner types I to VI. Young rabbits were given weekly injections of the antigen (preserved with 0.5 per cent phenol) beginning with 0.25 c.c. and increasing the dose in increments of 0.5 c.c. until a total of four or five injections was given. Such serum usually had a titer of 1:5,000 or 1:10,000. The serum was preserved with phenol-ether and diluted 1:10 for use. In this manner it was possible to make a tentative diagnosis of Flexner infection within 48 hours.

This procedure was then followed by more conclusive diagnostic procedures including biochemical reactions and typing with specific antisera. It is important to note that in some instances a culture from an apparently typical Kligler slope would give only a weak agglutination with the polyvalent serum, and on further study proved to be *Proteus rettgeri* (Rustigian and Stuart<sup>3</sup>). Because of the heavy inoculum used in the plating media employed it was found desirable to "purify" all cultures by replating on MacConkey's agar and selecting well isolated colonies. The biochemical examinations included the following media: Motility agar, tryptone broth with Kovac's reagent (for indol formation), gelatin stab, glucose, lactose, sucrose, mannitol, xylose, and dulcitol. The sugar broths were all made from a phenol-red broth base to which Seitz-filtered carbohydrate was added in amounts sufficient to give a concentration of about 0.5 per cent.

Typing was performed from a fresh agar slope. Although a large number of cultures was typed by the method advocated by Wheeler, i.e., using a saline emulsion from a fresh agar slope heated for one hour at 70° C.,<sup>4</sup> it was found that comparable results were obtained by emulsifying a small portion of the growth in a drop of saline on a slide and using this as the typing antigen. Also, no difficulty was experienced in typing *S. paradysenteriae* from the fresh original Kligler slopes that showed strong agglutination in the polyvalent serum. This was later adopted as a routine practice, followed in all instances, however, by a check with a purified culture.

In addition to the bacteriological examinations, fresh wet saline mounts of each stool specimen were examined for ova and parasites; no concentration methods were used. The presence of mucus, blood, or pus was also noted.

Hospitalized patients who had active infections with diarrhea had three to five stool examinations made at two to three day intervals with a final follow-up culture six to eight weeks after the onset of symptoms. Carriers had examinations made at two to four week intervals.

#### CLASSIFICATION OF DYSENTERY BACILLI

Within the past decade considerable advances have been made in the classification of dysentery bacilli. The earlier methods based on biochemical reactions alone have been supplemented by serological methods. At present classification depends upon both biochemical and serological reactions.

The genus *Shigella* is basically divided into *non-mannitol fermenters* and *mannitol fermenters* as follows:

A. *Non-mannitol fermenters.*

*Shigella*

1. *Shigella dysenteriae* or Shiga type. (Does not produce indol.)
2. *Shigella ambigua* or Schmitz bacillus. (Produces indol.)
3. Organisms of Sachs<sup>6</sup> and of Christensen and Gowen<sup>7</sup> which have recently been described.

B. *Mannitol fermenters.*

*Shigella*

1. *Shigella paradysenteriae* group which includes the Flexner and Boyd subgroups. (Members of these subgroups are essentially alike biochemically but serologically distinct.)
2. *Shigella sonnei*. (Similar in many respects to *S. paradysenteriae* but ferments lactose slowly. It does not produce indol.) There are two serological races of *S. sonnei*—Phase I and Phase II. This organism is serologically homogenous, showing no antigenic relationship with other *Shigella* species.
3. *Shigella alkalescens*. (Ferments xylose, dulcitol, and glucose, in addition to mannitol.) It is antigenically homogenous but shows cross reactions with the Boyd P274 (Boyd type III) organism. It was formerly considered to be non-pathogenic but it is now believed that it is pathogenic.
4. *Shigella dispar*. (Late lactose fermenter and indol producer; salicin is not fermented.) It is serologically heterogenous. This organism is not pathogenic.

The pioneer serological work of Andrewes and Inman<sup>8</sup> classified the mannitol-positive and non-lactose fermenting (Flexner) organisms as types V, W, X, Y, and Z. This system has been supplanted by more fastidious typing methods. Although a split is evident in the genus *Shigella* on the basis of ability to ferment mannitol, biochemical methods are not satisfactory in determining types encountered. Thus, the serological systems introduced by Boyd<sup>9</sup> and modified by Wheeler<sup>5</sup> have come to be the most logical and the easiest to apply. At present the *S. paradysenteriae* group is subdivided into the following subgroups and types:

- A. *Flexner subgroup.* Type I in this classification is equivalent to the V strain of Andrewes and Inman; type II to W; and type III to Z. Races X and Y are looked upon as degraded type II (W) forms. Thus, Wheeler recognizes type II-a with an antigenic formula of II, 1, 3, 4 (where the Roman numerals indicate the specific antigenic component and the Arabic numerals group factors common to several types). Strain Y is the degraded result of this type, having group components 1, 3, 4, but containing no specific factor.

Type II-b has the formula of II, 1, 7, 8, whereas the X strains have the same group structure (1, 7, 8) but are lacking the specific factor. Type IV is equivalent to Boyd 103; type V to Boyd P119; and type VI to Boyd 88. Boyd pointed out that his 88 organism has the same antigenic structure as the Newcastle-Manchester bacilli. The latter two strains are characterized by the ability to form a very small amount of gas in glucose, mannitol, and sometimes in dulcitol. Otherwise, their characteristics are typical of a true bacillary dysentery organism.

B. *Boyd subgroup*. Boyd also recognized six other *S. paradyserteriae* types which reacted very weakly or not at all in sera of the Flexner types. These strains (170, P288, P274, D1, D19, and D143) have been classified as Boyd types I to VI. They are apparently not common and were not encountered in our series.

#### LABORATORY OBSERVATIONS

The results of the stool examinations in the group of 264 POWs was as follows: (See chart 1.)

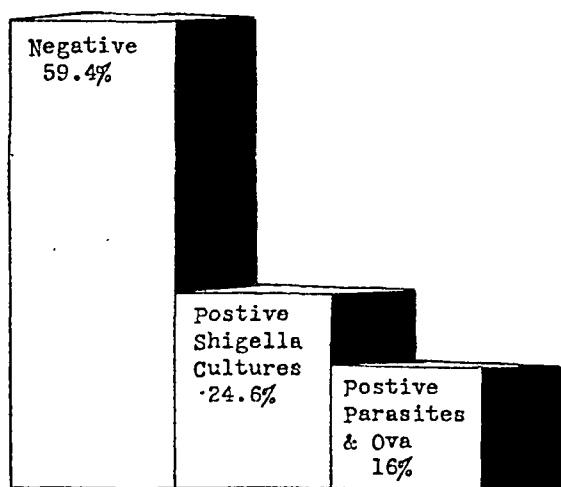


CHART 1. Positive stool findings in general group of prisoners of war.

|                                                 |                     |
|-------------------------------------------------|---------------------|
| Total number of POWs examined                   | 264                 |
| Number giving positive <i>Shigella</i> cultures | 65 or 24.6 per cent |
| Number showing parasites or ova                 | 42 or 16 per cent   |

*Bacillary Infections*. Of the entire group of 264 there were 60 patients who had symptoms compatible with a clinical diagnosis of dysentery (see chart 2). Some of these were admitted to the hospital for treatment and others were treated as out-patients. They varied from cases with mild symptoms to severe forms with considerable toxicity. Some arrived during the second week of their illness and had only residual symptoms that cleared up in a few days. Stool examinations in this group of patients were positive for *S. paradyserteriae* in 42 cases or 70 per cent. One patient had a

*Salmonella paratyphi B* infection, and another showed *Endameba histolytica* trophozoites without associated bacillary infection. Sixteen, or 26.6 per cent of the patients with diarrheal symptoms, had negative stool examinations. All of these patients probably had a *Shigella* infection but in some

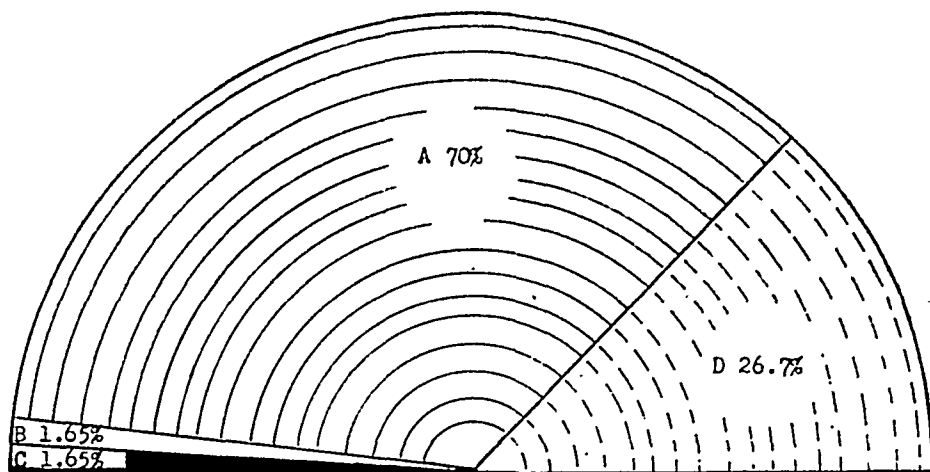


CHART 2. Results of stool examinations in clinical cases of dysentery. A. *S. paradyseriac*. B. *S. paratyphi* "B". C. *E. histolytica*. D. Negative.

instances stool specimens were not obtained until the later stages of the disease, and in others an insufficient number of stool specimens was obtained to be conclusive.

*Types of Dysentery Bacilli Isolated* (see chart 3). Only one non-mannitol fermenter and no Boyd types were found. Most of the *Shigella* organisms encountered were Flexner types. Individual types isolated in this series were as follows:

|                             |    |
|-----------------------------|----|
| <i>S. ambigua</i>           | 1  |
| Flexner type I              | 4  |
| Flexner type IIa            | 2  |
| Flexner type IIb            | 19 |
| Flexner type III            | 1  |
| Flexner type VI             | 30 |
| Flexner type X              | 2  |
| Flexner mixed types I & III | 1  |
| Sonne phase I               | 2  |
| Types undetermined          | 3  |

It is interesting to note that type VI was the common type in the first group examined in December, 1944, whereas type IIb was more common in the February, 1945, group.

Stools remained positive for about 7 to 12 days in the untreated cases whereas in the treated cases they were usually negative at the end of three to five days. Two patients, however, still had positive cultures at the end of eight weeks, and two chronic carriers still had positive stools eight weeks after the initial examination.

*Shigella Carriers.* Of the group of 65 positive cases 23 gave no history of diarrheal attacks of any kind for at least one year prior to examination, indicating that 8.3 per cent of the entire group were chronic carriers. It is quite possible that some of these carriers may have had subclinical dysentery and were actually convalescent carriers, but undoubtedly many of them were chronic healthy carriers. Some of them admitted having had clinical symptoms two or three years previously but had been free of recurrences. Wirts and Tallant<sup>10</sup> in a survey of American soldier food handlers in the middle East found the carrier rate to be 1.5 per cent among them and 4 per cent in

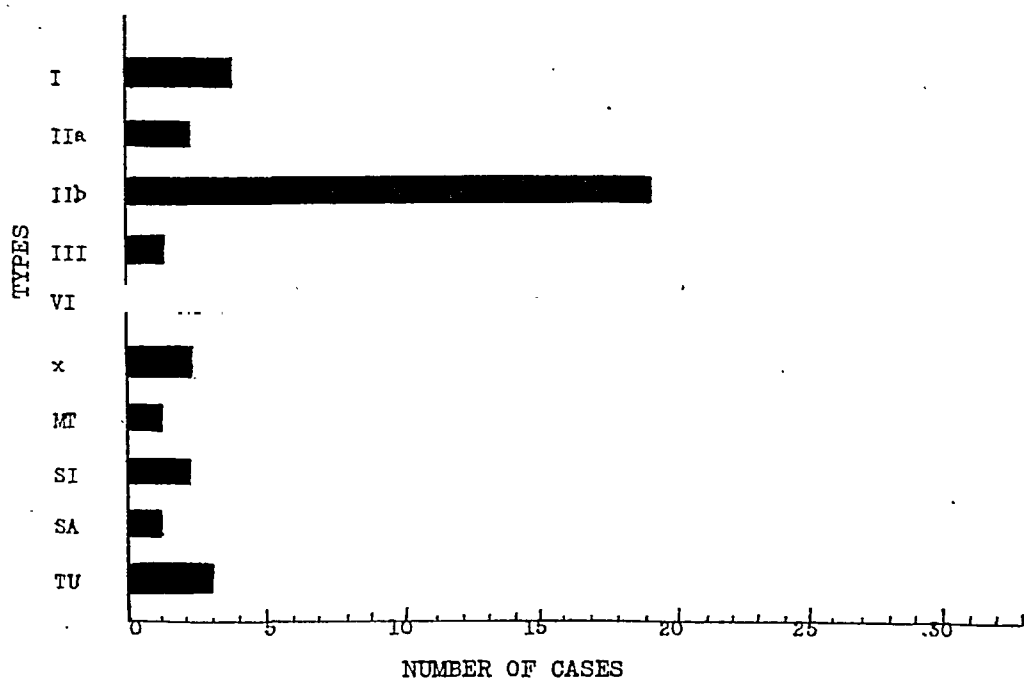


CHART 3. Types of *Shigella*. I, IIa, IIb, III, VI, and X. (Flexner Types.) MT—Mixed Types. SI—Sonne Phase I. SA—*Shigella ambigua*. TU—Type undetermined.

Sudanese native workmen. (Our own survey of 95 American soldier food handlers showed no incidence of *Shigella* carriers.) Most of the carriers had repeatedly negative stools following treatment with sulfaguanidine but two of them still had positive stools at the end of two months. In both instances the types recovered remained serologically identical with the organisms originally isolated, one being a Flexner II-a carrier and the other a Flexner VI. Two patients became convalescent carriers for at least eight weeks, both of these types remaining the same as the original infecting organisms, namely, type VI.

*Parasites.* Forty-two or 16 per cent of the total number of POWs that were examined showed one or more intestinal parasites or commensals. These were as follows:



|                                                                                                      |    |
|------------------------------------------------------------------------------------------------------|----|
| <i>Endameba coli</i> (cysts and trophozoites)                                                        | 20 |
| <i>Giardia lamblia</i> (trophozoites)                                                                | 3  |
| <i>Endolimax nana</i> (cysts)                                                                        | 3  |
| <i>Trichomonas hominis</i> (trophozoites)                                                            | 1  |
| <i>Iodameba bütschlii</i> (cysts)                                                                    | 1  |
| <i>Endameba histolytica</i> (trophozoites)                                                           | 1  |
| <i>Trichocephalus trichiura</i>                                                                      | 1  |
| <i>Ascaris lumbricoides</i>                                                                          | 2  |
| <i>E. coli</i> and <i>E. histolytica</i> (cysts)                                                     | 4  |
| <i>E. coli</i> (cysts) and <i>Ascaris lumbricoides</i>                                               | 1  |
| <i>E. coli</i> (cysts) and <i>Giardia lamblia</i> (trophozoites)                                     | 1  |
| <i>E. coli</i> (cysts) <i>Endolimax nana</i> (cysts) and<br><i>Trichomonas hominis</i> (trophozoite) | 1  |
| <i>Iodameba bütschlii</i> and <i>Endolimax nana</i> (cysts)                                          | 1  |
| <i>Trichocephalus trichiura</i> and <i>G. lamblia</i>                                                | 1  |
| <i>E. coli</i> (cysts) and <i>Endolimax nana</i> (cysts)                                             | 1  |

### SYMPTOMS

The symptomatology encountered was that chiefly associated with bacillary dysentery. In only one instance were symptoms attributed to *E. histolytica* per se. In the other three patients with *E. histolytica*, only cysts were demonstrated and bacillary infection was also found. The symptoms associated with *Giardia lamblia* were not constant; in some instances these patients had abdominal pain and mild diarrhea that cleared up following treatment with atabrine.

The symptoms of *S. paradysenteriae* infection varied from a very mild diarrhea with no other concomitant symptoms to severe diarrhea associated with vomiting and toxemia. There were no instances of fulminating cases characterized by high fever, dehydration, and severe melena such as frequently occurs with Shiga infections. In the majority of cases the onset was sudden with nausea, followed by severe vomiting, abdominal cramps, and diarrhea. The picture presented within one or two hours after the onset was that of persistent vomiting associated with urgent bowel movements. The average severe case had 10 to 15 stools during the first 24 hours. Stools were loose or watery and contained mucus; microscopic examination revealed the presence of red blood cells and pus. Only a few patients had an appreciable amount of gross blood in their stools. The average untreated case had frequent watery stools for one to two weeks. In some instances temporary periods of improvement occurred during which the patient would have three or four stools daily; this was followed by recurrences of 8 or 10 watery stools daily for four or five days, after which period the stools would return to normal number and consistency in most instances. A very distressing and persistent symptom was that of foul eructations. The mild cases had a mild diarrhea that lasted three or four days, gradually returning to normal within less than a week. In many instances the patient started out with mild symptoms for a few days followed by a two or three day interval during which apparent recovery seemed to have occurred and then would suddenly develop explosive symptoms as described above. The disease usually was self-limited and spontaneous recovery generally occurred within two to three weeks in the untreated cases.

## DIFFERENTIAL DIAGNOSIS

Several conditions must be considered in the event of an outbreak of gastrointestinal disorder, particularly diarrhea. The most important of these are as follows: (1) Acute gastroenteritis of a non-specific nature; (2) Bacillary dysentery (Shigellosis); (3) Salmonella infections (food poisoning); (4) Staphylococcus food poisoning; (5) Amebic dysentery; (6) Botulism.

In most instances the diagnosis is dependent entirely upon microscopic and cultural examinations of the stools. The history of the character of the food that may have been the cause and the type of onset are frequently of some help, although there is very little difference between the clinical picture of bacillary dysentery and that of food poisoning due to Staphylococcus toxin or to Salmonella. Both of the latter disturbances are usually of shorter duration than the Shigella infections. Botulism does not usually cause diarrhea and is associated with neurological disturbances such as double vision, muscular paralysis, and extreme weakness. A final diagnosis of either bacillary dysentery or Salmonella infections can be made only by proper microscopic and cultural examinations of the stools. The diagnosis of Staphylococcus food poisoning must frequently be made by elimination and by a history of the type of food. Staphylococcus toxin is usually encountered in custards, filled pies and cakes, cream puffs, or puddings. Unfortunately, the offending food is usually not available for culture by the time the outbreak occurs. It might be mentioned that the incubation period of Shigella infections is usually at least 24 hours and may be as long as three or four days, whereas Staphylococcus and the ordinary Salmonella food poisoning symptoms usually start within less than 24 hours, frequently occurring within two to six hours after ingestion of the offending food.

## TREATMENT

It is not the intent of this paper to go into details of treatment of these infections. Suffice it to say that sulfaguanidine and sulfadiazine were equally effective in causing rapid cure of the *S. paradysenteriae* infections. The dose of sulfaguanidine was 3.5 grams every four hours for the first two or three days and 3.5 grams every eight hours for the next three or four days, or, until patient was entirely symptom-free and had at least two negative stools. Sulfadiazine was given in the usual dosage of 2.0 grams initially, followed by 1.0 gram every four hours for the first two or three days; then 1.0 gram four times daily until symptoms disappeared and stools became negative.

*Endameba histolytica* infections were treated with emetine and carbarsone or chiniofon. *Giardia lamblia* was treated with atabrine.

## COMMENT

The results of this survey indicate that a large number of POWs harbor dysentery bacilli and may become potential sources of danger to other per-

sonnel. It is, therefore, important to keep a careful check on diarrheal outbreaks in POW camps and to treat all carriers. Usually these individuals were captured following a period during which they lived under extremely poor sanitary conditions and on an inadequate diet. Such conditions naturally cause a breakdown of resistance to infection and consequently they become easy prey to dysentery organisms transmitted by a few carriers. In turn, the number of carriers is increased and such groups become dangerous to others. Hardy and Watt<sup>1</sup> studied the diarrheal diseases in New Mexico, Georgia, New York City, and Puerto Rico and came to the conclusion that this group of diseases is becoming a major medical problem. They found a total of 76 per cent positive *S. paradyenteriae* stools in a series of severe endemic diarrheas in New Mexico and Georgia, and 56 per cent positive cases in milder types in those states. Forty-one per cent of the endemic cases studied in New York City were positive. The percentage of positives in older persons was higher than in infants. Serial cultures were made in 103 convalescents revealing 80 per cent to be carriers. The average duration of convalescent carrier state in their series was 34 days and about 10 per cent continued to remain carriers for more than 10 weeks. With rare exceptions the passive carrier state terminated in less than one year. They came to the conclusion that passive carriers are exceedingly rare.

Weil<sup>2</sup> agrees that the existence of dysentery carriers within the general population has been underrated. He cites the work of Bjolen in Denmark, and of McGinness, McLean, Spindle and Maxey in Virginia, both of which investigations confirmed the fact that bacillary dysentery infections are carried from one locality to another exclusively by man. He feels that contamination through flies is of only secondary importance although of more significance where the fly population is very large and means of protection against them are lacking. It is our own feeling that one of the reasons that dysentery is more prevalent during the warm months is that the food that has become contaminated with *Shigella* organisms is at a temperature more favorable to their growth. Consequently, the incubation period is shorter and bacterial growth more abundant.

The types of parasitic infections in the POWs that we examined were about the same as those in the civilian population in the same regions. A group of 82 civilian food handlers was examined by us and 41 or 50 per cent showed one or more of the following parasites:

|                                 |    |
|---------------------------------|----|
| <i>Endameba coli</i>            | 23 |
| <i>Ascaris lumbricoides</i>     | 17 |
| <i>Giardia lamblia</i>          | 8  |
| <i>Trichocephalus trichiura</i> | 7  |
| <i>Endolimax nana</i>           | 4  |
| <i>Endameba histolytica</i>     | 3  |
| <i>Enterobius vermicularis</i>  | 1  |
| <i>Iodameba bütschlii</i>       | 1  |

Bøe<sup>11</sup> examined over 1100 patients in the general medical and surgical wards of a hospital in Oslo. In 740 cases that showed no evidence of intestinal disturbances at least 50 per cent were infected with one or more intestinal amebae or flagellates. He encountered *Endameba histolytica* in 2.43 per cent of these cases and *Giardia lamblia* in 5.14 per cent. A high proportion of his patients carried non-pathogenic amebae (*E. coli* in 15.6 per cent and *E. nana* in 17.91 per cent). The impression he gained was that *Giardia lamblia* was not exactly innocuous as it was found more frequently in those cases with gastrointestinal symptoms. Our own experience coincides with these observations. Soper<sup>12</sup> also states that various intestinal protozoa usually regarded as non-pathogenic are actually able to cause intestinal derangement.

It is interesting at this point to note some observations made on a group of 34 Russians and Italians who were admitted to the hospital after release from German labor battalions. Most of these patients were admitted for non-enteric conditions; particularly tuberculosis and malnutrition. They had been living in extremely poor hygienic environment and were on a deficient diet for periods of one to three years. Of this group, nine had *Salmonella paratyphi B* infections (one of which was associated with *S. paradysenteriae*), and four had *S. paradysenteriae* (two, type VI; one, type V, and one undetermined type). One patient had an *E. typhosa* infection. A high percentage of them were infected with one or more parasites as follows:

|                                  |   |
|----------------------------------|---|
| <i>E. coli</i>                   | 8 |
| <i>T. hominis</i>                | 5 |
| <i>G. lamblia</i>                | 5 |
| <i>E. histolytica</i>            | 4 |
| <i>E. nana</i>                   | 3 |
| <i>Tr. trichiura</i>             | 3 |
| <i>Strongyloides stercoralis</i> | 2 |

In one case seven varieties of parasites and ova were recovered in addition to a *S. paradysenteriae*. These included *E. coli*, *E. histolytica*, *G. lamblia*, *Trichocephalus trichiura*, *T. hominis*, *E. nana*, and *Strongyloides stercoralis*. Others frequently contained three or four varieties of parasites.

#### SUMMARY

1. A stool survey was made on 264 prisoners of war.
2. Positive Shigella cultures were obtained in 24.6 per cent of the cases.
3. Parasites and ova were found in 16 per cent of the cases.
4. A large number of this group were found to be chronic carriers of Shigella organisms.
5. Convalescent and chronic carriers are a potential source of danger and should be thoroughly treated with the sulfonamides.

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# THE USE OF NEOARSPHENAMINE IN THE TREATMENT OF AMEBIC DYSENTERY \*

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THIS is to report 15 cases of amebic dysentery treated with neoarsphenamine intravenously during the Japanese internment of American Prisoners of War at Camp No. 1, Cabanatuan, Philippine Islands. This drug was not the drug of choice but rather the only drug at hand before the arrival of Red Cross medical supplies in December, 1943. Although neoarsphenamine had never been used to any appreciable extent for amebiasis, it was felt that the arsenic derived therefrom should be effective in eradicating the ameba and cysts. Arsenic is also a well known alterative, and it was believed that it would stimulate the appetite which was later found to be true.

Up to 1935, in a review of cases of amebiasis treated at the Mayo Clinic, it is stated that 38 patients received arsphenamine with no untoward reactions.<sup>1</sup> Six weekly doses of arsphenamine were given in those instances in which carbarsone, vioform or other drugs had failed to eradicate the ameba.

An in vitro study of mapharsen and seven other compounds has been recently conducted.<sup>2</sup> It was found that of the group of chemicals studied, three of which were known amebicides, mapharsen was the most effective, killing *Endameba histolytica* in 1 : 20,000 and 1 : 30,000 dilutions.

For the relief of acute dysenteries intravenous arsenicals have been used with considerable success and without the toxic side effects of emetine.<sup>3</sup> After a single injection of arsphenamine arsenic appears in the urine in a very few minutes. However, it is more slowly excreted in the feces and more than 50 per cent of that given is excreted by the alimentary tract.<sup>4</sup> Traces of arsenic are to be found in the liver, bile passages and bones for weeks after the cessation of therapy.<sup>5</sup>

## METHOD

The usual method of dissolving neoarsphenamine in distilled water was pursued. The distilled water was manufactured in the operating room using a home-made still, placed in rubber stoppered plasma bottles and boiled for 20 minutes to reduce the incidence of reactions. All cases were given a 0.3 gram dose. This relatively small dose was used because of the limited supply of the drug and because of the poor nutrition of the patients, most of whom were underweight or suffering from some vitamin deficiency.

The interval between doses was five days. Either three or four doses were given followed by a rest period during which microscopic examination

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of the stool was made. There being no facilities for stool culture, the diagnosis and the follow-up were dependent on the direct observation of material from warm stools, using the iodine staining method.

The cases were selected because the stools had remained positive despite treatment previously with various drugs which were at hand, such as small quantities of emetin, potassium iodide, mercury or thymol. Six of the 15 cases were in fairly good physical condition and remained so throughout the treatment. The other nine were markedly malnourished and almost all exhibited signs of vitamin deficiency. Those exhibiting such signs were given small quantities of vitamins if they were available. The undernourished were given two ounces of canned milk daily. Otherwise the diet of this series of cases was the same as that given the entire concentration camp, namely: steamed rice, carabao meat and vegetables, except that cooked liver was always saved for the dysentery patients as advocated by Kagy.<sup>6</sup>

## RESULTS

One striking result observed was a decrease in diarrhea. Patients, who had been having 11 or 12 bowel movements daily, showed a decrease to one to three daily movements. There was no increase in bowel activity during treatment and in only two cases did the diarrhea continue despite the treatment.

The physical condition of all 15 cases generally improved with the exception of two cases. Improvement consisted of increase in strength, increase in appetite, and several patients exhibited a gain in weight. Reactions to the intravenous injections were minimal, no more than would be expected when giving neoarsphenamine for syphilis.

| <i>Physical Condition</i> |     |          | <i>Bowel Activity</i>      |     |          |
|---------------------------|-----|----------|----------------------------|-----|----------|
|                           | No. | Per Cent |                            | No. | Per Cent |
| Improved.....             | 7   | 46       | Decreased.....             | 4   | 27       |
| Unimproved.....           | 2   | 13       | Increased.....             | 0   | 0        |
| Unchanged (Normal).....   | 6   | 41       | Unimproved (Diarrhea)..... | 2   | 13       |
|                           |     |          | Unchanged (Normal).....    | 9   | 60       |

Of the 15 cases treated, nine cases or 60 per cent had three or more subsequent negative stool examinations. On a check-up one year later it was found that two of these cases were positive and required further treatment. Following this, stools were negative. The remaining seven had remained well with no relapses for 12 months.

Of the six positive cases it was found on the one year check-up that three of them (cases 7, 12, and 14) received a second course of neoarsphenamine. Following this subsequent course of treatment stools were negative and the patients were in sufficiently good physical condition to be sent to duty with no subsequent relapses. Thus it can be reported that 12 of the 15 cases were successfully treated with neoarsphenamine.

The three unsuccessful cases remained in the hospital throughout the

## RESULTS

| Case No. | Previous Treatment                                  | Doses of Neoarsphenamine | Reactions                  | Bowel Activity | Subsequent Stool Microscopy | Physical Condition | Sigmoidoscopic Examination                              | Remarks                                            |
|----------|-----------------------------------------------------|--------------------------|----------------------------|----------------|-----------------------------|--------------------|---------------------------------------------------------|----------------------------------------------------|
| 1.       | Emetin, thymol, quinoxyl, mercury, potassium iodide | 4                        | None                       | Normal         | 5 Negatives                 | Remained normal    | None                                                    | Stool positive for cysts between 3rd and 4th doses |
| 2.       | Mercury, potassium iodide                           | 4                        | Nausea first dose<br>None  | Decreased      | 4 Negatives                 | Improved           | None                                                    | —                                                  |
| 3.       | Emetin, yatren, mercury, potas. iodide              | 4                        | None                       | Normal         | 4 Negatives                 | Improved           | None                                                    | Stool pos. for cysts between 3rd and 4th doses     |
| 4.       | Thymol, mercury, potassium iodide                   | 3                        | None                       | Normal         | 5 Negatives                 | Remained normal    | None                                                    | Gained 9 pounds                                    |
| 5.       | Thymol, mercury, potassium iodide                   | 3                        | None                       | Normal         | 6 Negatives                 | Improved           | None                                                    | Gained 3 pounds                                    |
| 6.       | Mercury, potassium iodide                           | 3                        | None                       | Normal         | 5 Negatives                 | Remained normal    | None                                                    | —                                                  |
| 7.       | Emetin, yatren, thymol, mercury, potas. iodide      | 3                        | None                       | Decreased      | Cysts of E. H.              | Improved markedly  | Red and indurated area in sigmoid. Smear pos. for cysts | Gained 5 pounds                                    |
| 8.       | Emetin—4 intramuscular and 6 oral doses             | 4                        | None                       | Decreased      | 4 Negatives                 | Improved           | Edematous dusky red area positive cysts                 | Gained 7 pounds                                    |
| 9.       | Yatren, potassium iodide                            | 3                        | Vomiting, nausea and fever | Normal         | 3 Negatives                 | Remained normal    | None                                                    | —                                                  |
| 10.      | Potassium iodide                                    | 3                        | Fever, loss of appetite    | Normal         | 8 Negatives                 | Improved           | None                                                    | —                                                  |
| 11.      | Emetin, thymol, potassium iodide                    | 4                        | None                       | Normal         | Cysts of E. H.              | Normal             | None                                                    | Stools neg. later following emetin and yatren      |
| 12.      | Emetin, thymol                                      | 4                        | None                       | Normal         | Cysts of E. H.              | Improved           | None                                                    | Gained 8 pounds                                    |
| 13.      | Emetin, carbarsonne, mercury                        | 4                        | Nausea                     | Diarrhea       | Cysts and Vegetative E. H.  | Unimproved         | Marked edema of mucous membrane                         | Appetite improved<br>Lost 16 pounds                |
| 14.      | Potassium iodide                                    | 3                        | Fever                      | Diarrhea       | Cysts of E. H.              | Normal             | None                                                    | —                                                  |
| 15.      | Yatren, potassium iodide                            | 3                        | None                       | Decreased      | Cysts of E. H.              | Unimproved         | None                                                    | —                                                  |



internment period and their stools were positive despite treatment with all available drugs received later in the shipment of Red Cross medical supplies.

### CONCLUSIONS

Neoarsphenamine is an effective drug in the treatment of amebiasis. Because of the inconvenience of intravenous administration, it probably does not enjoy the popularity of other arsenicals which can be given by mouth. From the writer's observation it would seem advisable to use somewhat larger doses and a longer course of treatment than were used in this series. At the least, neoarsphenamine is one more weapon available in those cases of amebiasis which are difficult to render stool negative.

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## STUDIES IN RHEUMATIC FEVER

### II. ABSORPTION OF SALICYLATES \*

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#### INTRODUCTION

ALTHOUGH salicylates induce striking symptomatic relief in rheumatic fever, especially in the presence of polyarthritis, the question of a more radical therapeutic action is a debated one. It has recently been suggested<sup>1</sup> that while small doses produce symptomatic relief only, large doses have a genuine curative effect. Our own data on this problem are analyzed in detail elsewhere.<sup>2</sup> The present paper is concerned with the technic of reaching the plasma or serum salicylate level of 20 to 30 mg. per cent or higher, which Coburn considered critical.

We have studied serum salicylate levels following oral, rectal and intravenous administration of sodium salicylate and of acetyl salicylate, the effect of concomitant administration of sodium bicarbonate,<sup>3</sup> differences in serum salicylate among groups supposedly receiving the same dosage, and the reasons therefor.

#### METHODS AND MATERIAL

The subjects included rheumatic fever patients and a number of normal volunteers.

Oral salicylate and bicarbonate were given in tablet form. In view of an unfortunate experience at another activity "enteric coating" was avoided. Intravenous sodium salicylate was given in 10 per cent solution. The drug was given rectally in solution of 50 gr. sodium salicylate in one ounce of water, care being taken that the solution was retained at least two hours.

The method outlined by Brodie, Udenfried and Coburn<sup>4</sup> was used for the determination of serum salicylates. A large series of comparative studies on the salicylate level of plasma and serum showed average difference of 2 mg. per cent.<sup>3</sup> As this difference was considered insignificant it was convenient to omit the oxalate and to do all determinations on serum. Since it was impossible to obtain a large supply of pyrex glass stoppered bottles we sought for an adequate substitute. The common 4 ounce "French Square"

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From the Laboratory and the Rheumatic Fever Service United States Naval Hospital, Corona, California.

bottle with a bakelite screwcap proved extremely satisfactory. The inner layer of cork and paraffin in the caps must be removed before use. Screw caps of plastics other than bakelite are dissolved by ethylene dichloride and therefore cannot be used. Thirty-six to 50 bottles can conveniently be shaken at one time in the ordinary Kahn Shaker. Ethylene dichloride is toxic and should be used only with forced ventilation. Since ethylene dichloride should not be pipetted, it may be measured from a tapered graduated cylinder holding 30 ml.

## RESULTS

Serum salicylate levels in normal volunteers at various intervals after ingestion of 50 grains (3.3 gm.) are shown in tables 1 to 4. It is evident

TABLE I  
Serum Salicylates Mg. per cent  
Normal Subjects  
50 Grains Sodium Salicylate

|    | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. | 48 Hrs. |
|----|----------|---------|---------|-------|--------|--------|--------|---------|---------|
| RC | 0        | 3       | 8       | 14    | 17     | 21     |        | 9       | 0       |
| RH | 0        | 14      | 21      | 21    | 15     | 17     | 14     | 6       | 0       |
| IE | 0        | 3       | 10      | 15    | 23     | 22     | 21     | 12      | 0       |
| BS | 0        | 13      | 24      | 26    | 26     | 18     | 19     | 8       | 0       |

TABLE II  
Serum Salicylates Mg. per cent  
Normal Subjects  
50 Grains Sodium Salicylate  
50 Grains Sodium Bicarbonate

|    | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. | 48 Hrs. |
|----|----------|---------|---------|-------|--------|--------|--------|---------|---------|
| RC | 0        | 9       | 16      | 21    | 22     | 21     | 17     | 11      | 0       |
| RH | 0        | 10      | 12      | 18    | 19     | 20     | 16     | 3       | 0       |
| IE | 0        | 9       | 18      | 24    | 29     | 27     | 21     | 15      | 0       |
| BS | 0        | 12      | 13      | 16    | 24     | 22     | 20     | 11      | 0       |

TABLE III  
Serum Salicylates Mg. per cent  
Normal Subjects  
50 Grains Acetyl Salicylate  
50 Grains Sodium Bicarbonate

|    | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. | 48 Hrs. |
|----|----------|---------|---------|-------|--------|--------|--------|---------|---------|
| EC | 0        | 2       | 8       | 10    | 7      | 8      | 6      | 0       | 0       |
| IP | 0        | 19      | 17      | 18    | 19     | 17     | 15     | 1       | 0       |
| CA | 0        | 13      | 19      | 15    | 8      | 2      | 6      | 1       | 0       |
| VS | 0        | 3       | 6       | 10    | 10     | 10     | 13     | 0       | 0       |

TABLE IV  
Serum Salicylates Mg. per cent  
Normal Subjects  
50 Grains Acetyl Salicylate

|    | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. | 48 Hrs. |
|----|----------|---------|---------|-------|--------|--------|--------|---------|---------|
| HS | 0        | 2       | 4       | 8     | 10     | 20     | 20     |         |         |
| W  | 0        | 1       | 2       | 3     | 6      | 15     | 16     |         |         |
| ES | 0        | 1       | 4       | 8     | 16     | 30     | 9      |         |         |
| PC | 0        | 3       | 4       | 6     | 11     | 11     | 14     |         |         |

that levels of 19 mg. per cent are quickly and readily obtained. In many instances there was considerable circulating salicylate at 15 minutes and height of the curve did not appear significantly modified by the concomitant administration of 50 gr. sodium bicarbonate. In all instances blood levels were zero at 48 hours. Corresponding figures following administration of 30 grains sodium salicylate intravenously are shown in table 5. When administered without bicarbonate, acetyl salicylate was evidently absorbed more slowly than sodium salicylate.

TABLE V  
Serum Salicylates Mg. per cent  
Normal Subjects  
30 Grain Sodium Salicylates  
Intravenously

|    | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. | 48 Hrs. |
|----|----------|---------|---------|-------|--------|--------|--------|---------|---------|
| RH | 0        | 18      | 18      | 15    | 13     | 11     | 13     | 2       | 0       |
| RC | 0        | 28      | 21      | 19    | 16     | 15     | 9      | 5       | 0       |
| IE | 0        | 24      | 23      | 20    | 20     | 19     | 18     | 8       | 0       |
| BS | 0        | 20      | 20      | 18    | 17     | 16     | 13     | 4       | 0       |

In marked contrast are the results of administration by rectum (table 6). Three patients with rheumatic fever who had been off salicylates for three days were each given 50 grains sodium salicylate by rectum immediately after the withdrawal of a "control" blood specimen. This dosage was repeated three times at four hour intervals so that a total of 200 grains was given by rectum during the day. However, the serum salicylate level did not rise above 7 mg. per cent. Salicylates were discontinued for three days.

TABLE VI  
Serum Salicylates Mg. per cent  
Rheumatic Fever Patients  
Rectal Administration (V. Text)

|   | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 23.5 Hrs. |
|---|---------|-------|--------|--------|--------|-----------|
| M | 0       | 1.5   | 1.2    | 0      | 0      | 0         |
| S | 0       | 2     | 5      | 7      | 3.5    | 4         |
| F | 0       | 3     | 3      | 1      | 0      | 0         |

then resumed by mouth in a daily dosage of 100 grains aspirin and 100 grains bicarbonate. On this oral dosage these men attained serum salicylate levels of 16 to 20 mg. per cent.

In studies on rheumatic subjects it was evident that the salicylate level, if moderately high before the test dose, could be raised only slightly by oral or intravenous administration. The persistently low levels shown by a few of the subjects were not explained (tables 7 and 8).

TABLE VII  
Serum Salicylates Mg. per cent  
Rheumatic Fever Patients  
25 Grains Sodium Salicylate

|   | Pre Dose | 15 Min. | 30 Min. | 1 Hr. | 2 Hrs. | 4 Hrs. | 24 Hrs. |
|---|----------|---------|---------|-------|--------|--------|---------|
| J | 12.5     | 13      | 13      | 13    | 22     | 19     | 14      |
| B | 10       | 10      | 10      | 11    | 12     | 14     | 6       |
| L | 9        | 7       | 11      | 12    | 15     | 15     | 15      |
| H | 29       | 26      | 28      | 33    | 29     | 30     | 18      |
| M | 27       | 27      | 28      | 33    | 26     | 26     | 24      |
| S | 26       | 30      | 30      | 32    | 31     | 26     | 30      |

25 grains of sodium salicylate were administered every four hours except at 16 and 20 hours.

TABLE VIII  
Serum Salicylates Mg. per cent  
Rheumatic Fever Patients  
30 Grains Sodium Salicylate  
Intravenously

|   | Pre Dose | 15 Min. | 30 Min. | 90 Min. | 2 Hrs. | 4 Hrs. | 8 Hrs. | 24 Hrs. |
|---|----------|---------|---------|---------|--------|--------|--------|---------|
| C | 32       | 38      | 37      | 35      | 35     | 32     | 27     | 23      |
| P | 30       | 35      | 32      | 32      | 30     | 29     | 25     | 15      |
| D | 10       | 20      | 21      | 19      | 18     | 26     | 18     | 16      |
| S | 27       | 34      | 33      | 29      | 29     | 19     | 30     | 27      |

25 grains sodium salicylate by mouth were administered every four hours except at 16 and 20 hours.

The effect of the drug on the cerebration of normal subjects was of some interest and importance. The symptoms experienced by one of us (R.W.H) were typical: nausea, lightheadedness, garrulity and irresponsibility were quite comparable to those which follow ingestion of alcohol, though the elation characteristic of the latter drug was absent. As one of the subjects observed, a salicylate jag is quite a melancholy affair. Dizziness was common shortly after administration of the drug and was most conspicuous when the rise in serum salicylate was abrupt. It was usually absent at two hours, even when the serum salicylate level was maximal.

It was evident that large doses of salicylate were not pleasant to take and that they induced a state of irresponsibility. In a study of daily serum salicylate levels it was noted that the levels were, with one exception, consistently high in a group of young officers, while in a group of enlisted men,

supposedly on the same dosage, several showed decided irregularities. It seemed that this difference was most readily attributable to greater conscientiousness on the part of the officer group on taking the prescribed medication. An officer who was asked to explain a sudden drop in his serum salicylate level stated: "Doctor, I knew how important it was for you and for me that I should keep on taking that stuff but somehow I just couldn't bring myself to do it so I told the nurse she'd better take it out last night before I threw it away." Inquiry revealed that the enlisted men whose irregularities were striking were in the habit of putting their tablets under their pillows. A comparison of serum salicylate levels of enlisted men on two wards, all supposedly on 120 grains (8 gm.) of acetyl salicylate daily, showed much greater consistency and higher average level on the ward which had the more efficient and experienced nurse (figure 1).

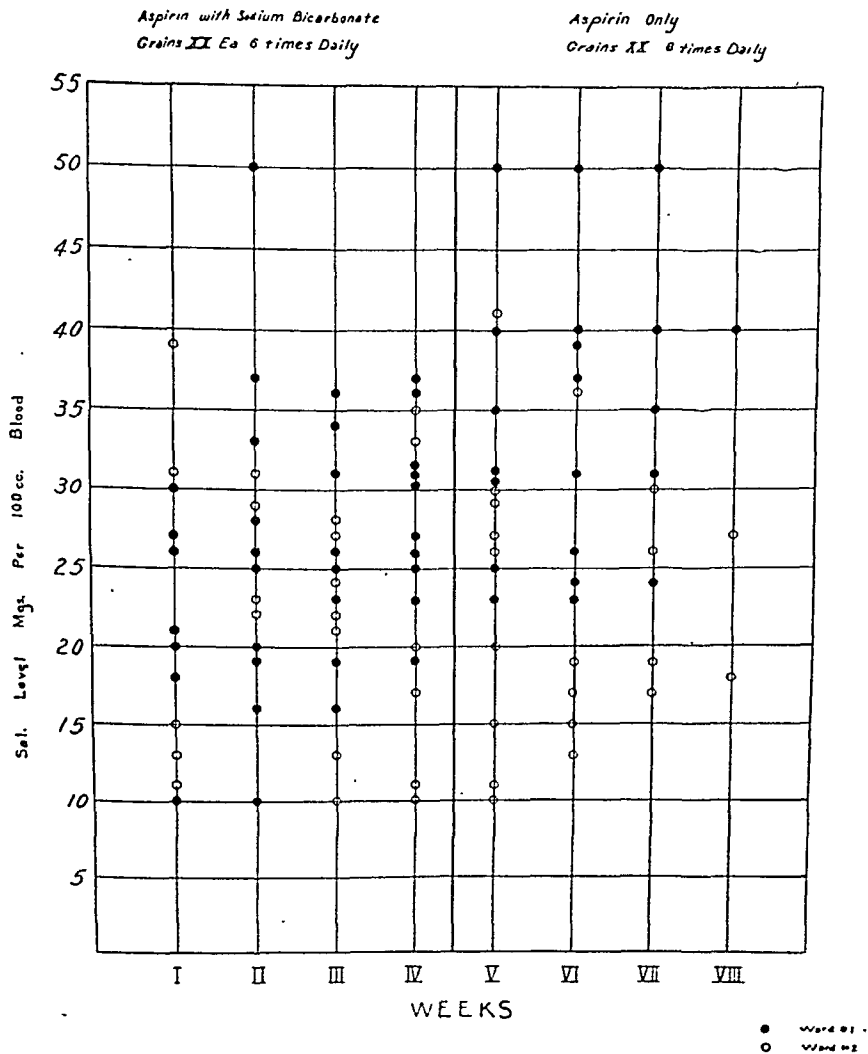


FIG. 1.

# Salicylate Level Mg. Per 100 C.C. Blood

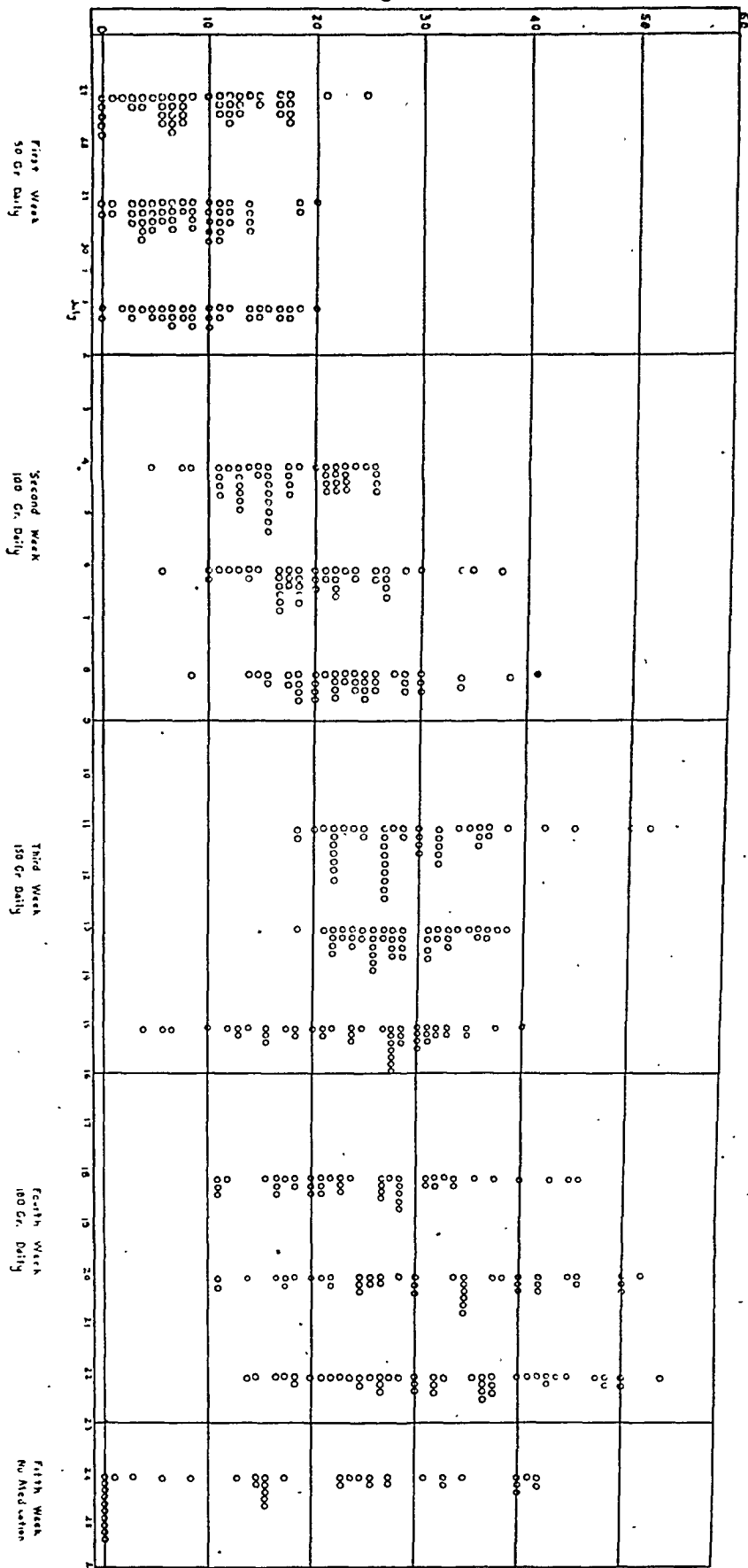


FIG. 2.

With these experiences in mind, it was interesting to go back to data on serum salicylate levels on various dosages in our first large scale experiment.<sup>5</sup> The men (rheumatic fever patients) had all volunteered for this experiment and its importance had been carefully explained to them. The figures suggest that coöperation was good until the fourth week, when some of the group began to show irregularities (figure 2).

Observations on carefully supervised patients on 150 grains (10 gm.) sodium salicylate daily did not suggest that the daily administration of 60

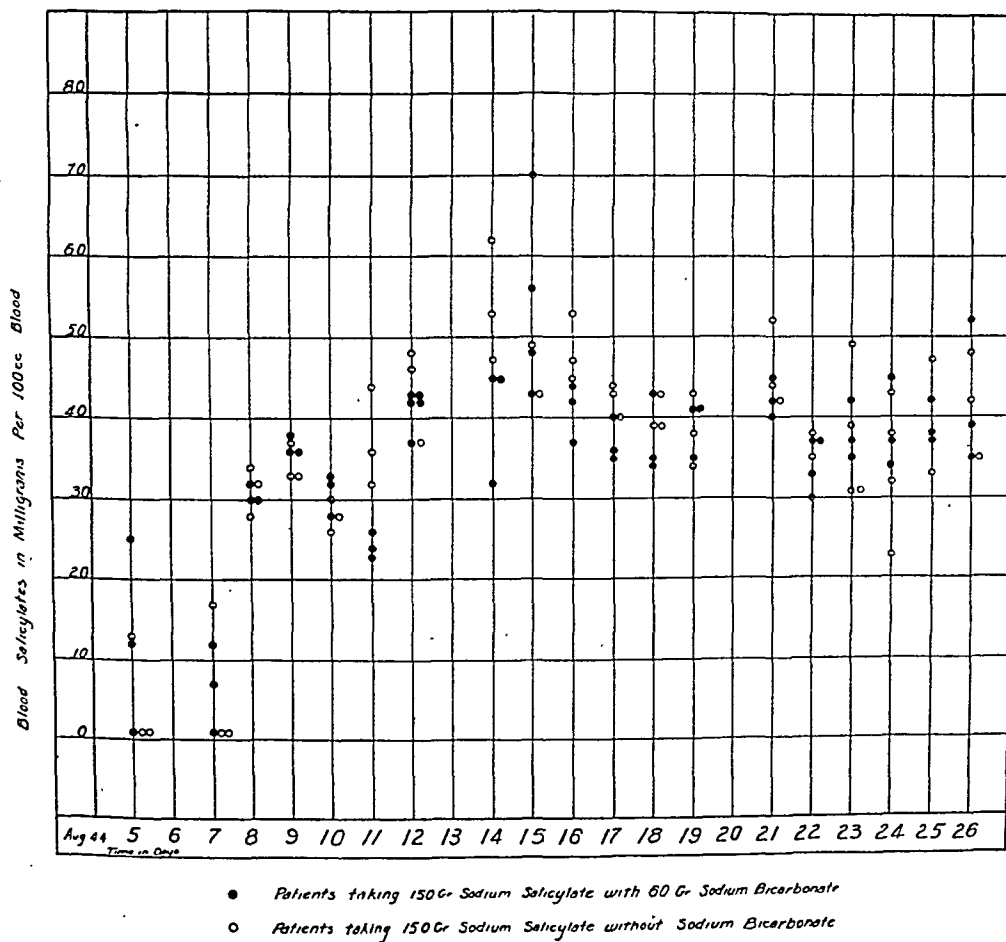


FIG. 3.

grains (4 gm.) of sodium bicarbonate affected the serum salicylate level (figures 3 and 4). Two of the patients given 150 gr. sodium bicarbonate likewise showed no change. Possibly a more extended trial with this dosage would have shown changes similar to those recorded by Smull.<sup>3</sup> However, in order to duplicate her technic we should have had to resort to enteric coating of salicylate tablets. In practical salicylate administration we see no reason for giving more than 60 gr. (4 gm.) of sodium bicarbonate daily.

Although detailed discussion of therapeutic data will be reserved for



another paper,<sup>2</sup> it is well to mention that therapeutic failures occurred alike among those with consistent high blood levels and those with irregularities suggestive of irresponsibility in taking the medication.

DISCUSSION

The assumption that medication prescribed is synonymous with medication taken is particularly unsafe with salicylate on account of its gastric and cerebral side effects. Such effects would probably be more conspicuous in subacutely ill patients than in the febrile toxic patients described by Coburn.<sup>1</sup> On the whole it seems evident that most of the men took their medication in

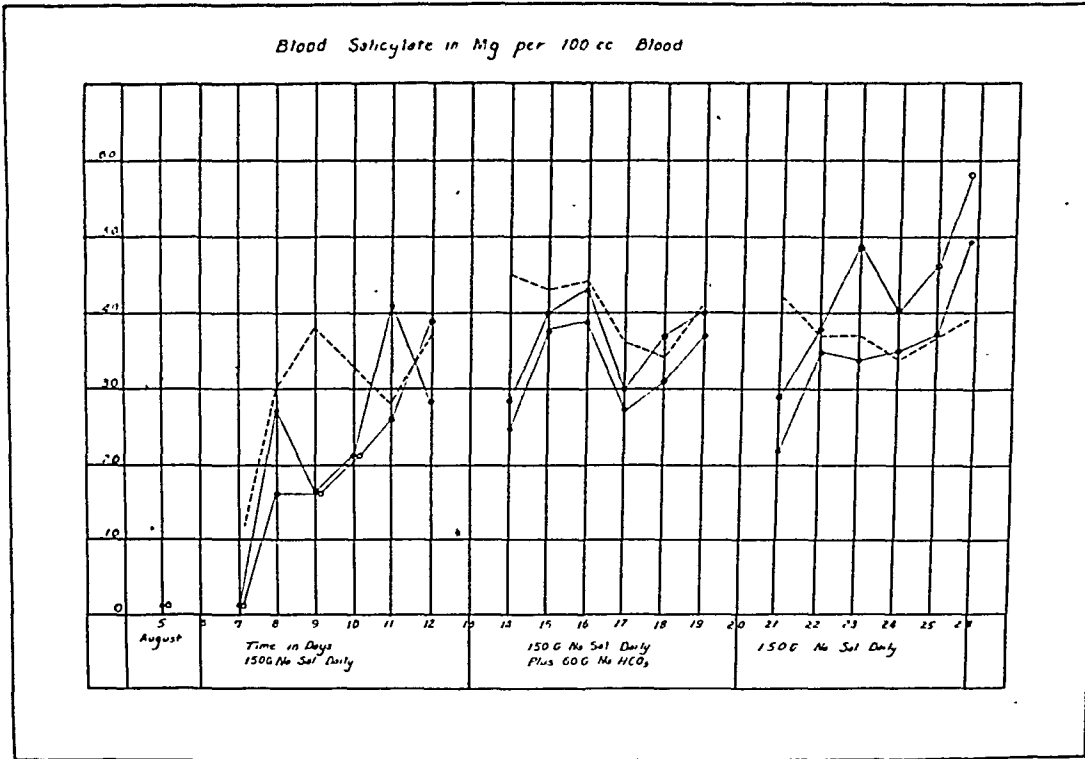


FIG. 4.

a commendably conscientious manner. The problem of those who did not is one for sober clinical consideration, not for invective.

Our observations show salicylate to be readily absorbed from the upper end of the gastrointestinal tract and poorly absorbed from the lower. Thus we believe that salicylate should not be given in enteric coated tablets, nor by rectum. With administration of ordinary tablets by mouth, gastric irritation can be minimized by simultaneous administration of food or bicarbonate.

Bicarbonate sufficient for this purpose did not, in our experience, cause a definite reduction in serum salicylate level. Since clinical acidosis has been extremely rare among our patients on salicylate, we feel that daily dosage of

bicarbonate need not exceed 60 gr. (4 gm.). Salicylate levels have been well maintained on such a regimen. Our technic differs from that of Smull in that she used enteric coated salicylate tablets and larger doses of bicarbonate. These differences doubtless account for differences in results.

Our findings have not driven us to frequent intravenous administration of salicylate. Certain considerations against this procedure are more pertinent with our material than with that of Coburn. Our "typical" relapse was characterized not by high fever with polyarthrititis but by low grade fever with cardiac failure. The undesirability of giving large infusions with cardiac failure is generally recognized and concentrated salicylate solutions have a marked sclerosing action. Absorption from the gastrointestinal tract is prompt, and we have seldom had difficulty in maintaining a suitable serum level on oral administration if the drug is actually swallowed. Severe congestive failure has some effect on gastrointestinal absorption but seems to contraindicate intravenous administration.

It is of interest, however, that in a patient with reticuloendothelial leukemia whose recurrent polyarthrititis was clinically indistinguishable from that of severe rheumatic fever, relief was said to be much more striking after intravenous than after oral salicylate. One can only speculate as to the reasons for this. As already noted, certain toxic manifestations seem to be associated with a sharp rise in serum salicylate level rather than with its maintenance. Possibly a similar relation might hold with certain analgesic and anti-pyretic effects. The possibility that gastrointestinal absorption might produce pharmacologically important changes not detectable in the determination of serum salicylate level cannot, of course, be denied.

#### SUMMARY AND CONCLUSIONS

1. Since large doses of salicylate are unpleasant to take and induce irresponsibility comparable to that of alcohol, supervision is necessary to insure that the medication is taken. With very few exceptions apparent irregularities in absorption or excretion have in our experience turned out to be irregularities in ingestion.

2. Salicylate is absorbed well from the upper gastrointestinal tract and poorly from the lower intestinal tract. Rectal administration of salicylate is cumbersome and inefficient and enteric coating of tablets given by mouth seems contraindicated.

3. Gastric irritation can be minimized by simultaneous administration of food or sodium bicarbonate. For this purpose small doses of sodium bicarbonate are sufficient, and such doses are without significant effect on the serum salicylate level.

4. Differences between our results and those of Smull<sup>3</sup> are doubtless due to her use of enteric coated tablets and of large doses of bicarbonate.

5. Our experience does not tend to justify frequent intravenous administration of salicylate.

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# THE TREATMENT OF RHEUMATIC FEVER BY ROENTGEN-RAY IRRADIATION \*

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## INTRODUCTION

It is an accepted medical fact that in the absence of a specific therapeutic agent for a given disease entity there are many non-specific methods of treatment proposed. Because of the prevalence of rheumatic fever and the urgency in wartime to marshal only the best of the available therapeutic armamentaria, an evaluation of roentgen-ray irradiation in rheumatic fever is apropos.

From 1926 to 1933 the most significant studies in this field were published by Levy and Golden.<sup>1</sup> A careful review of the literature concerning the effects of roentgen irradiation on the heart was published by the same authors.<sup>1b</sup> In this summary of the literature, it was stated that only one of numerous postmortem studies showed damage to the myocardium sufficient to denote specific roentgen-ray injury. In rabbits and in dogs irradiated with moderate doses, the only clinical sign of damage noted was transitory premature contractions; with larger doses, cell necrosis, hemorrhage and proliferation of connective tissue were found in the auricular musculature.

One of us referred 17 rheumatic fever patients over a nine year period for roentgen-ray treatment. The roentgenologist followed the technic described by Levy and Golden.<sup>1b</sup> No clinical or electrocardiographic improvement was seen in the treated group differing from that seen in an untreated similar age group. The minor changes seen in the electrocardiogram after roentgen irradiation were seen as frequently in the untreated group. Therefore, it seemed wise to select a large group of patients who could be observed for six to 12 months.

## SOURCE OF MATERIAL

The Rheumatic Fever Unit at the U. S. Naval Hospital, Corona, California, with its large census of patients under the care of well-trained cardiologists is the source of material for this study.

Two hundred and twenty-nine patients, all of whom had been ill with a well established rheumatic fever of six months' or more duration were selected as subjects by the ward medical officers. Twenty-eight of the 229 patients did not complete the prescribed course of treatment. Therefore, the final number studied totaled 201 patients. Three of the 28 patients were

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dropped from the study because of untoward symptoms attributed to the roentgen-ray reaction. One patient complained of precordial heaviness and two complained of excessive nausea. Twenty-five patients were lost through discharge from the service or through transfer to a convalescent unit too far removed for continuance of the study.

### METHOD OF STUDY

Before the roentgen-ray therapy was instituted, a careful evaluation of the history, physical examination and laboratory studies was made of each patient by the ward medical officer in association with the director of the study. A similar evaluation was made of the 201 patients at the end of 12 weeks and 42 patients at the end of 26 weeks. The evaluation consisted of a careful review of the history, a recheck of the physical examination, the clinical course and comparison of weekly electrocardiograms and blood sedimentation rates.

All routine treatments such as rest, diet, salicylates, heliotherapy, educational, occupational and physical therapy were continued.

At the direction of the roentgenologist, the 201 patients were divided into three groups:

- Group A received 100 r through the myocardium at weekly intervals for five successive weeks.
- Group B received 100 r through the myocardium and over the middle and lower cervical sympathetic ganglia every week for five successive weeks.
- Group C received no treatment but went through the same mechanical routine as groups A and B. A lead filter was used to block out the roentgen-rays.

A well-trained roentgen-ray technician carried out the above-outlined schedule. Neither the roentgenologist, the clinicians, nor the patients knew into which group individual patients were placed by the technician.

After the five-week schedule of treatments and the 12-week reevaluations were completed, the patients were listed as to groups and classified as to "No Improvement," "Very Slight Improvement," "Moderate Improvement" and "Marked Improvement." At the end of 26 weeks 42 patients were available for a similar review and classification.

### RESULTS OF THE STUDY

Of the 201 patients studied 56 (or 27.8 per cent) patients had one or more attacks of rheumatic fever prior to enlistment.

From table 1 it can be determined that after 12 weeks there was no significant change in Group A (treated through the myocardium) and Group B (treated through the myocardium and cervical ganglia) different from that found in Group C (untreated group).

TABLE I  
Effects of Irradiation—After 12 weeks

| Group                   | A           | B          | C          |
|-------------------------|-------------|------------|------------|
| No Improvement          | 35 = 49.4%  | 41 = 65.0% | 40 = 59.7% |
| Very Slight Improvement | 21 = 29.5%  | 16 = 25.4% | 20 = 29.8% |
| Moderate Improvement    | 14 = 19.7%  | 5 = 7.9%   | 7 = 10.4%  |
| Marked Improvement      | 1 = 1.4%    | 1 = 1.6%   | 0 = 00.0%  |
| Totals                  | 71 = 100.0% | 63 = 99.9% | 67 = 99.9% |

Similarly, those patients available for review and classification after 26 weeks showed no significant differences in the three groups.

TABLE II  
Effects of Irradiation—After 26 weeks

| Group                   | A          | B          | C         |
|-------------------------|------------|------------|-----------|
| No Improvement          | 6 = 40.0%  | 7 = 58.3%  | 6 = 40.0% |
| Very Slight Improvement | 7 = 46.6%  | 4 = 33.3%  | 6 = 40.0% |
| Moderate Improvement    | 2 = 13.3%  | 1 = 8.3%   | 3 = 20.0% |
| Marked Improvement      | 0 = 00.0%  | 0 = 00.0%  | 0 = 00.0% |
| Totals                  | 15 = 99.9% | 12 = 99.9% | 15 = 100% |

Table 3 shows the 201 patients grouped according to the types the rheumatic fever assumed.

TABLE III  
Types of Rheumatic Fever Patients Treated

| Total Rheumatic Fever Patients Ill for 6 Months | 201 | 100%  |
|-------------------------------------------------|-----|-------|
| Type IV—Acute Fulminating                       | 9   | 4.4%  |
| Type III—Subacute Polycyclic                    | 55  | 27.3% |
| Type II—Subacute Monocyclic                     | 127 | 63.1% |
| Type I—Subclinical                              | 10  | 4.9%  |

From table 4 it is noted that irradiation did not appear to be more helpful in those patients with acutely active rheumatic fever than in those patients with mildly active rheumatic fever.

It has been stated by Levy and Golden that best results were obtained in those patients treated during the primary attack. Table 5 shows no significant improvement in those patients treated during the primary attack over the group of patients who had one or more previous attacks of rheumatic fever.

TABLE IV  
Effects of Irradiation upon Types

| Types  | Number     | No Improvement | Very Slight Improvement | Moderate Improvement | Marked Improvement |
|--------|------------|----------------|-------------------------|----------------------|--------------------|
| IV     | 9 patients | 9 = 100%       | 0                       | 0                    | 0                  |
| III    | 55 "       | 30 = 54.5%     | 19 = 34.5%              | 5 = 9.0%             | 1 = 1.8%           |
| II     | 127 "      | 71 = 55.9%     | 36 = 28.3%              | 19 = 14.9%           | 1 = 0.7%           |
| I      | 10 "       | 6 = 60.0%      | 2 = 20.0%               | 2 = 20.0%            | 0                  |
| Totals | 201 "      | 116            | 57                      | 26                   | 2                  |

TABLE V  
Effect upon Patients with Primary Attacks Compared with Recurrent Attacks

|                                   | No Improvement | Very Slight Improvement | Moderate Improvement | Marked Improvement |
|-----------------------------------|----------------|-------------------------|----------------------|--------------------|
| 145 patients with primary attacks | 72 = 49.9%     | 36 = 24.0%              | 26 = 17.0%           | 11 = 7.5%          |
| 56 patients with E.P.T.E. status  | 22 = 39.3%     | 14 = 25.0%              | 12 = 21.4%           | 8 = 14.3%          |

### SUMMARY

1. Two hundred one patients who had been on the sick list with rheumatic fever for six or more months were classified as to the type of attack and degree of activity.

2. The 201 patients were divided into three groups: Group A received 100 r through the myocardium; Group B received 100 r through the myocardium and over the middle and lower cervical ganglia; Group C received no roentgen-ray exposure.

3. No significant change in the degree of the rheumatic fever activity was noted in any of the three groups.

4. Reëvaluation at the end of 12 weeks and 26 weeks showed no greater improvement in the treated groups over the untreated group.

5. There was no demonstrable therapeutic value from roentgen-ray therapy in the primary or in the recurrent attacks of rheumatic fever.

6. It is believed that roentgen-ray therapy is not a useful procedure in the treatment of rheumatic fever.

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## REITER'S DISEASE: A REPORT OF TWO CASES\*

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REITER'S disease may be defined as a syndrome of unknown etiology, characterized by urethritis, conjunctivitis, and arthritis, with a tendency to recurrence.<sup>1</sup> Two cases of this disease were encountered by the authors during the past year. They are being reported in this paper because they demonstrate certain features not previously described, because the literature on the subject is scant, and because many of our colleagues have shown themselves to be unaware of the existence of this syndrome, which may be readily confused with gonorrhea, rheumatic fever, the common type of infectious arthritis, and various local disorders of the genito-urinary tract, eyes and skin.

The diagnosis of Reiter's disease depends entirely upon the clinical picture and this will be briefly reviewed. Up to the present the disease has been recognized in young adult males only. At times a history of promiscuous sex contact shortly before the onset of symptoms is obtained; more frequently this is lacking. The presenting symptoms are urethral discharge, burning on urination and frequency. The discharge is purulent and suggests a gonococcus infection, but smears and cultures are negative for gonococci. As the disease progresses, extension to the posterior urethra, prostate, bladder and, possibly, the upper urinary tract may occur.<sup>3</sup>

Several days after the onset of the urethritis (3 to 13 days in our cases) a conjunctivitis or polyarthritis makes its appearance. Either may occur initially, or the onset of both may be simultaneous. The conjunctivitis is purulent and diffuse. Spread to the sclerae and corneae is not uncommon and corneal ulcerations have been reported.<sup>5</sup> The urethritis and conjunctivitis frequently subside completely in several days or several weeks, but, as in all manifestations of Reiter's disease, exacerbations and recurrences are common. Even after apparent complete recovery, there may be a return of symptoms as long as two years later.

Although the genito-urinary and ocular symptoms give rise to great discomfort, it is the arthritis that accounts for most of the disability. Almost any joint in the body may be affected. Pain is severe and is associated with marked tenderness of the joint and of the periarticular bones. Edema, limitation of motion, and spasm of adjacent muscles are present as in the common variety of infectious arthritis. After several months, degenerative bone changes appear in the roentgenogram. In our cases, which were followed

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The opinions in this article are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the service at large.



for a period of about six months, arthritic changes persisted, and it appears probable that these patients have a chronic arthritis indistinguishable from other types.

The cases presented illustrate the usual characteristics of this disease, together with some features not previously reported.

#### CASE REPORTS

*Case 1.* J. H. D., a naval officer 31 years of age, was admitted to a naval hospital November 11, 1943 with chief complaints of a urethral discharge, backache and painful swellings of the hands and left ankle. Five days before admission, without previous sexual exposure, he developed a yellow urethral discharge, with frequency of urination and fever. Upon admission, the discharge had largely subsided, the frequency and fever had persisted. Two days before admission, painful red swellings occurred in a single metacarpophalangeal joint of each hand, followed by lumbar backache and a painful tender redness and swelling of the left ankle.

The past history revealed that the patient had returned from Casablanca five months before admission. Three weeks before admission he had fallen and injured two fingers of the right hand, in one of which the acute painful swellings had begun. There were no other illnesses of significance; venereal disease or exposure was denied. The family history was non-contributory; the patient was married and had three children.

Physical examination on admission revealed the patient to be in excruciating pain, with a fever of 101°. Findings were normal except for a slight yellow mucopurulent urethral discharge and the involved joints, which were red, swollen and acutely tender. The day following admission, there appeared a number of small superficial ulcerations of the penis and a severe conjunctivitis, associated with a yellow purulent discharge. The same day the right shoulder and toes of the right foot became acutely painful and tender. There were no cardiac murmurs at any time.

Laboratory examinations gave no clue as to etiological factors. Urethral and prostatic smears and cultures were negative for gonococcus, the urethral cultures were reported as containing gram positive cocci and diplococci, with an occasional gram negative extracellular diplococcus. Cultures of the prostatic secretions and the penile lesions showed a non-hemolytic staphylococcus. Cultures of the urine were negative repeatedly. Dark field examinations of the penile lesions were negative for spirochetes. The blood Kahn and gonococcus complement fixation tests were negative. The blood cultures and agglutination tests for typhus, typhoid, paratyphoid and undulant fever were negative. Electrocardiograms were within normal limits.

Routine urinalyses on admission showed albumin and pus cells up to 300 per high power field. The pyuria, with traces of albumin and hyalin and granular casts, persisted for some weeks and disappeared only after a course of 600,000 units of penicillin. The blood counts were within normal limits except during the acute stage of the disease. At this time there was leukocytosis of 19,000, the differential count remaining within normal limits. A moderately severe secondary anemia, which developed at this time, was treated with three transfusions of 500 c.c. each. The sedimentation rates were normal on admission and discharge; during a period in which the patient had symptoms of acute rheumatoid arthritis the rate was 30 mm. in one hour (Cutler method).

During hospitalization the clinical course was characterized by persistent fever and severe multiple joint pains, as well as the formation of numerous ulcerations in various parts of the body. An intermittent fever of 101° to 102° persisted for a month, and gradually subsided during the following month. Severe pain was associated with ulcerations of the eyes and mouth; the ulcers elsewhere were painless

The ulcers in different areas were similar in character. Multiple small yellowish vesicles would form; these would gradually spread, become superficially ulcerated and in many areas confluent (figure 1). Multiple lesions of this character occurred in the palpebral conjunctivae, the cornea, hard palate, pharynx, penis, scrotum and palms of the hands. Ulcerations of the cornea were followed by corneal opacities, which gradually cleared up with the restoration of normal vision. Lesions which developed on the soles of the feet differed from the others in that they resembled pustules with hyperkeratosis of the overlying skin (figure 2). Incision of these lesions, however, showed only heavy cornification. These lesions became deeply ulcerated, resulting in the desquamation of the entire surface of the feet coming into contact with the floor. The finger nails finally became thickened, brittle, and developed heavy keratotic deposits under them. This condition gradually improved with treatment.



Fig. 1. Penile lesions of case 1, illustrating the beginning ulceration of the vesicles, the spreading superficial character and the final confluence.

The arthritic symptoms were the predominating feature of this case. The pain in the swollen left ankle was present, with variable severity, for approximately five months. The pain in the right shoulder persisted for several months; during the first month severe pain on motion prevented any voluntary active motion of the arm. An acute pain in the left knee began one week after admission. This was associated with considerable swelling, especially in the supra-patellar area and acute tenderness, especially over the upper third of the tibia. A severe painful spasm of the hamstring muscles with a resulting contracture of the knee required the application of a plaster cast for several weeks. Two weeks after admission severe pain developed in the left temporo-mandibular joint, with tenderness and inability to chew solid foods for a period of a month.

The arthritic problem of greatest practical importance involved the hands. Intermittent pain, redness, and swelling occurred in various metacarpophalangeal joints during a period of four months. The swelling in these joints gradually subsided, especially following two courses of penicillin (totalling one million units) and produced no deformities. One month after admission, contractures of the ring and little

fingers of the left hand developed, which were relieved by manipulation and the temporary application of a banjo splint. Fusiform swellings of the proximal interphalangeal joints of the fingers recurred intermittently for a period of weeks, finally subsiding, except for a residual spindle-shaped enlargement and ankylosis in the ring and little fingers of the right hand. The terminal interphalangeal joints in the involved fingers were also somewhat enlarged.

Roentgenogram of the right hand, taken 10 days after admission, was negative for evidence of fracture or other disease. Roentgenogram of the hands 10 weeks after admission showed demineralization of the bones of the hands and wrists, narrowing of the joint spaces of the proximal interphalangeal joints, and some destruction of the proximal phalanges of these fingers. Roentgenogram of the left ankle and foot showed only demineralization, without joint changes. Subsequent roentgenograms showed an improvement in the demineralization, except in the involved fingers, in which there was further destruction and ankylosis of the proximal joints.



FIG. 2. An early stage in the development of the yellow hyperkeratotic lesions of the feet in case 1. Later these lesions became more numerous, enlarged, ulcerated and confluent. Complete desquamation of all weight-bearing surfaces was followed by healing.

All methods of treatment were necessarily symptomatic; codeine and aspirin for relief of pain were the only measures which gave any definite results. Two courses of sulfonamides, sulfathiazole and sulfadiazine, had no effect. No result was obtained from a course of neoarsphenamine, given on empirical grounds. The results of penicillin treatment, two courses totalling one million units being given six weeks and four months after admission, were somewhat more encouraging. There was some temporary improvement noted during these courses of treatment, in the relief of joint swelling and pain, clearing of the pyuria, a tendency for the fever to subside, and an improvement in the sense of well-being of the patient.

Generally speaking, the acute stage of this distressing and painful disease lasted about three months, during which time joint pains, anemia, toxemia, weakness, and physical disability were severe. A gradual improvement in the general condition was associated with severe circulatory disturbances of the previously painful joints, which became cold and cyanotic when the patient resumed the upright position. The final condition of the patient upon discharge for sick leave, six months after admission, was

good, except for the deformity and stiffness of the fingers of the right hand, which were typical of rheumatoid arthritis.

*Case 2.* E. F. L., a man aged 24, a sergeant in the U. S. M. C., was admitted to a Naval Hospital on March 7, 1945 complaining of pain in the right shoulder, left wrist and left foot of six days' duration. The patient's illness began on February 14 with dysuria and urethral discharge, a week after sexual exposure without prophylaxis. Urethral smears were negative for gonococci. Sulfathiazole 0.5 gm. t.i.d. was given for four days without relief of symptoms. On February 27 both eyes became inflamed, with burning, itching, redness, and a thick discharge that caused the lids to stick. The joint pains appeared two days later.

The patient had had a similar illness in March 1943, at which time he was in Australia. Symptoms appeared a month after the last sexual exposure, in which prophylaxis had not been used. As in the present attack, smears were negative for gonococci, and sulfonamide therapy caused no improvement. Conjunctivitis appeared 10 days after the onset of the illness and arthritis seven days later. The patient recovered and returned to duty after a total illness of three months. The past history and family history were otherwise non-contributory.

Physical examination upon admission revealed a well-developed and well-nourished man, complaining bitterly of pain in the affected joints. The temperature was 102° F. The left wrist and dorsum of the left foot were slightly swollen and exquisitely tender. There was tenderness and limitation of motion of the right shoulder, and tenderness over the right sternoclavicular junction and both sacroiliac joints. Both conjunctivae were congested and showed a yellow purulent discharge. The urethral meatus was reddened, and a moderate amount of milky material could easily be expressed. The prostate was diffusely enlarged, but not tender.

The laboratory studies demonstrated a hemoglobin of 14.4 gm., a red blood cell count of 4,930,000, and a white blood cell count of 16,450, with 75 per cent polymorphonuclears, 20 per cent lymphocytes and 5 per cent eosinophiles. The sedimentation rate was 16 mm. in one hour by the Cutler tube method. Urethral and conjunctival smears and cultures were negative for gonococci, revealing non-hemolytic *Staphylococcus aureus*, hemolytic *S. aureus*, hemolytic and non-hemolytic streptococci, diphtheroids and tetrads. Wet mounts of pus were negative for protozoa, and the stool was negative for ova and parasites. Blood culture was negative, as was the gonococcus complement-fixation test. Agglutination tests for *B. abortus* and *E. typhosa* were repeatedly negative. Electrocardiograms and roentgenograms of the chest revealed no significant findings. Roentgenograms of involved joints were negative except for decalcification of the bones of the right wrist after three months of illness.

Treatment with penicillin was begun on March 15, 1945 and 700,000 units were given intramuscularly over a period of four days, but there was no apparent benefit. The patient ran an intermittent fever between 98° and 102° F. for five months. His weight dropped from 140 to 95 pounds. A moderate secondary anemia developed and was treated with two transfusions of 500 c.c. of citrated blood, each of which was followed by a transient urticaria. The patient's urethritis was complicated by prostatitis and cystitis, the latter causing some hematuria. Old urethral strictures, probably due to the attack of 1943, were discovered. Intravenous urography was negative. All genito-urinary symptoms had disappeared after four months. The conjunctivitis persisted for two months and was complicated by an area of scleritis, which did not ulcerate. About a month after the subsidence of the conjunctivitis, symptoms returned in milder form for a week. The arthritis spread to involve the left sternoclavicular joint, the right wrist, the left hip, both knees, and the spine. Five months after the onset of illness, pain and limitation of motion continued to be present in the right shoulder, lumbar spine and both wrists.

On April 14 a generalized lymphadenopathy was noted for the first time, with involvement of the cervical, axillary, epitrochlear and inguinal lymph nodes. The spleen could not be palpated. The blood count remained unchanged. On April 24 an inguinal lymph node was excised. Microscopic section showed only a non-specific type of hyperplasia (figure 3) and culture of the lymphoid tissue was negative except for diphtheroids.

During his fifth month of illness the patient developed a number of keratotic lesions on the dorsum of both hands, and the finger nails were raised by accumulation of keratotic material (figure 4). Culture of these lesions revealed hemolytic *Staphylococcus aureus* and smears were negative except for an occasional white blood cell.



FIG. 3. An area of the central portion of a lymph node in case 2, showing a moderate infiltration with plasma cells and some engorgement in the lymph sinuses surrounding the blood vessels and lymphatics.

A persistent eosinophilia was noted throughout this patient's illness. The total white cell count ranged from 9700 to 19300 and the eosinophiles between 2 and 28 per cent, falling below 5 per cent in only two counts.

*Comment:* All attempts up to the present time to determine the cause of Reiter's disease have been unsuccessful, although spirochetes, enterococci, staphylococci, and a filterable virus have been suspected by various authors. The abundant purulent discharges from the urethra and conjunctivae have yielded a heterogeneous group of bacteria of the varieties commonly found in these tissues as contaminants. Blood cultures have been consistently negative. Culture of an excised inguinal lymph node in one of our cases was also disappointing, as only diphtheroids, regarded as not significant, were isolated. Bauer and Engleman<sup>2</sup> cultured excised synovial membrane of an involved joint with equally negative results.

Notwithstanding the unknown etiology, the disease described by Reiter in 1916<sup>1</sup> appears to constitute a definite clinical entity, and the two cases presented in this paper are fairly typical. The fact that two cases were seen by the authors within a year, together with the fact that Rosenblum<sup>5</sup> collected 10 cases within a relatively short time, would seem to indicate that the disease is not as uncommon as the paucity of the reported cases suggests. In all probability, lack of familiarity with the syndrome has caused a number of cases to be overlooked.



FIG. 4. Fingernail lesions in case 2 showing nails thickened and broken, with accumulations of keratotic material beneath the nails and excoriation of the surrounding areas of the fingers. Similar lesions occurred in case 1.

Case 1 illustrates the skin and mucous membrane lesions of Reiter's disease better than does case 2. These made their appearance 10 days after the onset of the illness and eventually cleared up entirely. The outstanding feature of this patient's illness was his prolonged, disabling, extremely painful arthritis, which left the patient with several stiff fingers having the usual appearance and roentgen-ray findings of rheumatoid arthritis. To the best of our knowledge, this permanent disability has not been reported previously. Hyperkeratotic collections were found beneath the fingernails in both cases. Lever and Crawford<sup>4</sup> have suggested that keratosis blennorrhagica may occur in Reiter's disease, and our cases would seem to confirm this concept. Kuske<sup>9</sup> concurs in this opinion, but believes that the possibility of pustular psoriasis must be considered.

The second of our cases was unusual in that a generalized lymphadenopathy was found and the pathologic picture of an excised inguinal lymph node is presented in figure 3. The occurrence of such adenopathy is not

surprising in a disease with manifestations as widespread as those of Reiter's disease, but no previous report of such involvement has come to our attention. The same case showed a fairly high eosinophile count, the significance of which is not clear. Studies of stool specimens and purulent material from the urethra and eyes for protozoal infestation were unrevealing. Skin lesions resembling keratosis blennorrhagica appeared relatively late and were limited to the hands. These are illustrated in figure 4. Another finding of note in case 2 is the presence of urethral strictures, attributed to the patient's first attack, which antedated the second by two years. The urethritis in this case spread to involve the prostate and bladder, but the upper urinary tract was normal on intravenous urography. Colby<sup>3</sup> has reported dilatation of the renal pelves and ureters in this disease. Postma<sup>6</sup> has considered the penile lesions (see figure 1) similar to those of balanitis circinata. This author and Baldan<sup>7</sup> have also reported gastrointestinal symptoms which were not encountered in our cases.

Our experience in the treatment of Reiter's disease has paralleled that of others.<sup>8</sup> Adequate doses of sulfonamides and of penicillin were given with little avail. In case 1 neoarsphenamine was also used without benefit. Supportive treatment with transfusions, analgesics and local antiseptics gave symptomatic relief.

#### SUMMARY

1. The clinical picture of Reiter's disease is reviewed and two cases presented.

2. The disease, characterized by urethritis, conjunctivitis and arthritis, is of unknown etiology and has a tendency to recur.

3. Skin and mucous membrane lesions are described. The former resemble keratosis blennorrhagica.

4. Generalized lymphadenopathy is reported for the first time and biopsy of an inguinal lymph node described.

5. Permanent ankylosis of the fingers, resembling rheumatoid arthritis, occurred as an unusual complication in one case.

6. Attempts at specific therapy with sulfadiazine and penicillin were unsuccessful, although the latter drug apparently resulted in temporary improvement in one case.

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# SPONTANEOUS MEDIASTINAL EMPHYSEMA \*

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KNOWLEDGE of the pathology and clinical signs of emphysema of the interstitial tissues of the lung and the mediastinum dates from the time of Laennec, but only during the past decade has it been realized that such emphysema may occur in the absence of thoracic trauma or infection. Full credit is due to Hamman for the recognition and description of mediastinal emphysema of apparently spontaneous origin. In 1934, Hamman<sup>1a</sup> described three cases of this syndrome, later adding four others.<sup>1b, 1c</sup> Since that time, the medical literature has included sporadic reports of similar cases. The experimental work of Macklin<sup>2</sup> has contributed greatly to the elucidation of the pathogenesis and pathologic physiology of this syndrome.

It is our purpose to record the histories of three patients with spontaneous mediastinal emphysema whom we have observed, and to analyze all the reported cases from a clinical point of view.

## CASE REPORTS

*Case 1.* A 24 year old white male, a merchant seaman by occupation, was admitted to the hospital on June 30, 1944, complaining of dyspnea and precordial pain of two days' duration. On June 28, 1944, while driving a car, the patient suddenly developed severe, sharp, precordial pain radiating to the entire left anterior chest area, associated with dyspnea. The pain was aggravated by inspiration and erect posture. A friend gave the patient three pills of undetermined nature, and, after taking them, he lost consciousness for about 20 minutes. An infrequent nonproductive cough developed and persisted, with the pain and dyspnea, until admission to the hospital. There had been no previous similar episodes, and the past history and family history revealed no pertinent data.

Physical examination on admission revealed a husky young man, six feet tall, weighing 175 pounds, and moderately dyspneic. Decreased mobility of the left side of the chest, with hyperresonance, diminished breath sounds and vocal fremitus over the left lung indicated the presence of a pneumothorax on the left. Cardiac dullness could not be elicited. The heart sounds were of normal quality and there were no murmurs. The rhythm was of sinus origin, and the heart rate was 100 per minute. The blood pressure was 104 mm. Hg systolic and 82 mm. diastolic. Except for dental caries, the rest of the physical examination was not remarkable. There was no subcutaneous emphysema. The temperature was normal.

Urinalysis, Kahn reaction, sedimentation rate, and blood count were not remarkable. The white blood cells numbered 9,150 per cu. mm. and the differential count was normal. A roentgenogram of the chest indicated about 60 per cent collapse of the left lung. The right lung field appeared normal, and there was no evidence of air in the mediastinum in the postero-anterior projection.

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With use of analgesics, and other symptomatic measures, the pain and dyspnea subsided rapidly. On the day after admission, fine crackling sounds were heard over the precordium, occurring mainly during the systolic phase, and audible in all positions. The patient was not conscious of these sounds or of any unusual sensation. Further observation and studies could not be carried out because, since the patient felt fine, he could see no reason to remain in the hospital.

*Case 2.* A 38 year old white male, an orchestra leader and composer by profession, was referred by his local physician with a diagnosis of acute pericarditis. During the evening of November 2, 1944, while conducting his orchestra, he experienced a rather severe pain in the interscapular region radiating upward into the neck. There had been no preceding respiratory infection, and no unusual exertion. The pain gradually increased in intensity, and radiated to the substernal area, where it localized. By midnight, the pain had become so severe that the patient was unable to continue his work. He retired to his bed, where he noted that if he lay on his left side, a peculiar grating sensation was present in the precordial area. The past history was not pertinent, and there had been no previous similar attacks.

Physical examination at that time revealed a temperature of 99.2° F. (37.3° C.). The pulse was regular and full, with a rate of 84 beats per minute. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. Percussion of the chest revealed no abnormalities. Cardiac dullness was not altered. A grating sensation was transmitted to the palpating hand over the precordium, and was most marked when the patient was in the left lateral position. On auscultation, loud, rasping or crunching sounds were audible throughout the cardiac cycle over the entire precordium, with slight respiratory variations in intensity. The lungs were clear, and the rest of the examination was not remarkable. A hypodermic of morphine and atropine was given with resultant complete relief of the pain. The patient was seen again on the following day at noon. He was comfortable and had not had a recurrence of the pain. Physical examination at this time revealed no abnormalities. There were no adventitious sounds. The heart rate, rhythm, and sounds were normal. The blood pressure was 124 mm. Hg systolic and 80 mm. diastolic. The leukocyte count was 8,000 per cubic millimeter with a normal differential, and the sedimentation rate was normal. Roentgenograms of the chest on November 3, November 5, and November 9, 1944 showed no abnormalities. Electrocardiograms taken on two successive days, and including multiple chest leads, were normal. Physical examination, chest roentgenogram, and electrocardiogram one month after the episode were all normal.

*Case 3.* A 20 year old white male junior medical student had been playing volleyball on November 13, 1944, and, two hours after the game, noted rather sharp, moderately severe pain in the region of the cardiac apex. The pain radiated around to the left subscapular area and up into the left shoulder; it was aggravated by deep inspiration and by recumbency, particularly in the left lateral position. There was no dyspnea, nausea, vomiting, palpitation, or collapse. Concomitant with the pain, the patient became conscious of a peculiar crepitant sensation in his chest along the left border of the sternum, and heard fine crackling sounds emanating from the same area, which were loudest in left lateral recumbency. The pain and the crackling were relieved by the erect position or right lateral recumbency. A few days previously, the patient and several of his classmates had heard a brief discussion of mediastinal emphysema in section teaching, and they made the correct diagnosis in this instance immediately.

The past history was of interest in that when the patient was 14 years old he had had a somewhat similar episode, with severe pain in the left chest developing after an extremely deep inspiration, while playing a trombone. The same crackling sounds were heard by the patient at that time, and the pain and crackling lasted for six or eight hours and were followed by inspiratory precordial pain which persisted for

three or four days. A physician at that time made the diagnosis of pleurisy and strapped the chest with adhesive. One year later, when he was 15 years old, the patient had another similar episode, but was unable to recall details.

The patient was seen by us on November 14, 1944, the day after the onset. The pain had persisted, but was not incapacitating. Physical examination revealed no evidence of acute distress. The patient was a tall, thin young man, six feet and four inches tall, weighing 160 pounds. The cardiac apex was within the mid-clavicular



FIG. 1. Chest roentgenogram in Case 3, taken November 15, 1944 demonstrating the line of air alongside the right border of the cardiac shadow and the left pneumothorax.

line, and the heart sounds were of normal quality. The rhythm was of sinus origin, and the rate was 80 per minute. The blood pressure was 98 mm. Hg systolic and 72 mm. diastolic. Loud, sharp, crackling and crunching sounds were audible through the stethoscope over the entire precordium when the patient was recumbent, especially in the left lateral position, occurring both in the systolic and diastolic phases, but more marked during systole. Fluoroscopic examination of the chest and lateral roentgenograms on November 14, 1944 showed no evidence of free mediastinal air or pneumothorax. The evening of the same day, while the patient was walking home from a movie, he noted sudden accentuation of the pain in the precordial area, with

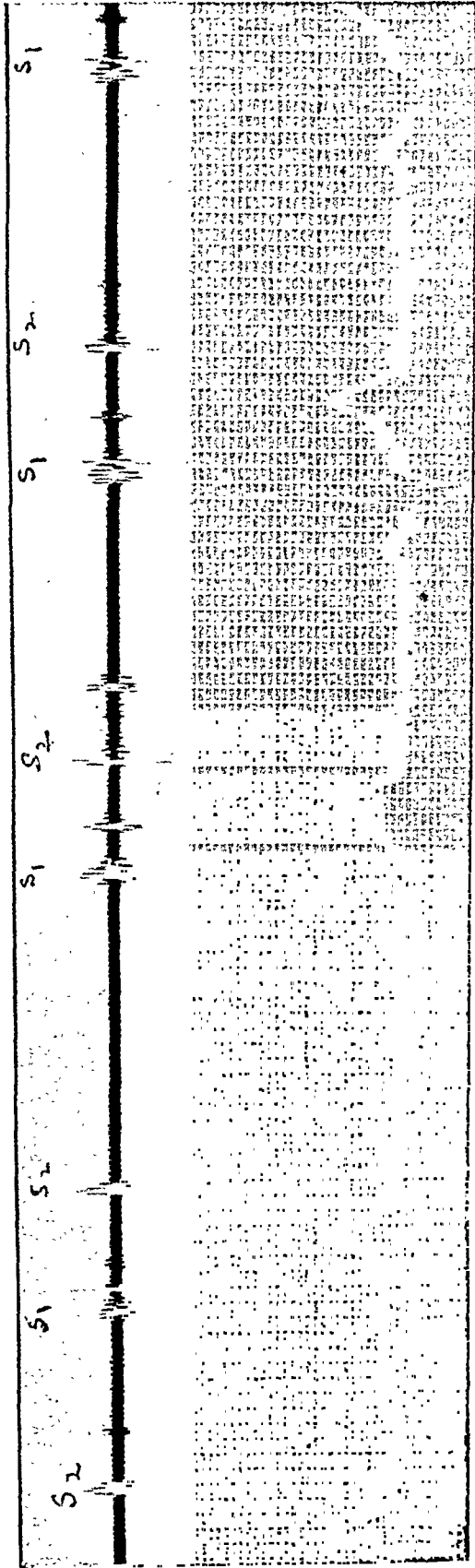
radiation through to the back, and on the following morning the physical signs of a pneumothorax on the left side were present. A roentgenogram of the chest confirmed these signs and the patient was hospitalized. Urinalysis and blood count were normal. The white cells numbered 7,350 per cubic millimeter and the differential count was normal. Treatment was symptomatic, and the course was afebrile and uneventful. The crackling sensation and sounds disappeared by November 17, 1944, and the left lung had completely reexpanded by December 4, 1944. Reexamination on January 8, 1945 revealed no abnormalities. The blood pressure was 108 mm. Hg systolic and 74 mm. diastolic. Electrocardiograms and stethocardiograms in this case are reproduced in figures 1 to 3.

### PATHOGENESIS

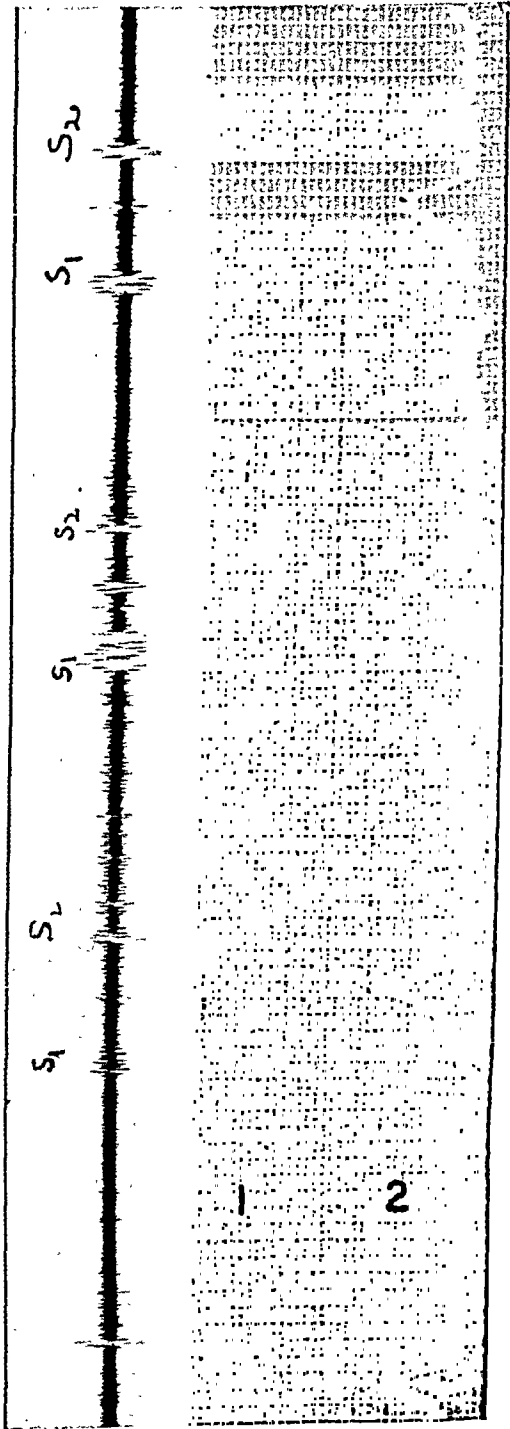
Laennec, in his book on auscultation published in 1831,<sup>3</sup> described the peculiar respiratory crackling sounds characteristic of interstitial emphysema of the lungs. In 1856, Rokitansky<sup>4</sup> included a description of traumatic mediastinal emphysema in his textbook on pathology, but the earliest discussion of the pathogenesis of mediastinal emphysema which is consistent with our present concept is found in the writings of Müller,<sup>5</sup> who in 1888 summarized the course of events as follows: "As a result of forceful coughing, disruption of the pulmonary alveoli may occur . . . the air then becoming compressed in the interstitial tissue of the lung. The bubbles of air then may progress to the hilus of the lung in the connective tissue investing the bronchi or pulmonary blood vessels, and thence into the mediastinum, or the air bubbles may infiltrate beneath the pleura, lifting the pleura in the form of blebs, and then migrate to the hilus subpleurally. Thus, the loose meshes of the mediastinum are gradually infiltrated with air. The pericardium and the great vessels, as well as the trachea and esophagus, become surrounded by air bubbles, and, not infrequently, the emphysema also spreads between the parietal pleura and the ribs, extending to the insertion of the diaphragm, where it apparently always stops. . . . Often, but by no means in all cases, the collection of air, following the trachea and the great vessels, spreads to the left or (less often) the right supraclavicular fossa, as a crepitant subcutaneous swelling, extending from there to involve a large part of the body surface with subcutaneous emphysema." Müller also described the presence of crepitant sounds dependent upon the heart beat, and the diminution of the area of cardiac dullness in mediastinal emphysema.

The recent experimental work of Macklin<sup>2</sup> has confirmed some of these features, and has extended greatly our knowledge of the pathogenesis of interstitial and mediastinal emphysema. By a series of clearcut demonstrations, Macklin has proved conclusively that pulmonic interstitial emphysema in the experimental animal is practically synonymous with pulmonic perivascular emphysema, and that the transport of air from the alveoli to the mediastinum takes place in the sheaths of the pulmonary blood vessels. The sheaths of the bronchi and bronchial blood vessels are apparently not involved in this transport. Increased intrapulmonary pressure produced by inserting a catheter into a bronchus of an experimental animal and blowing

APEX—LEFT BRANCH ALLOCUTING



APEX—SUPINE



APEX—LEFT LATERAL RECUMBENCY (SPEED HALVED)

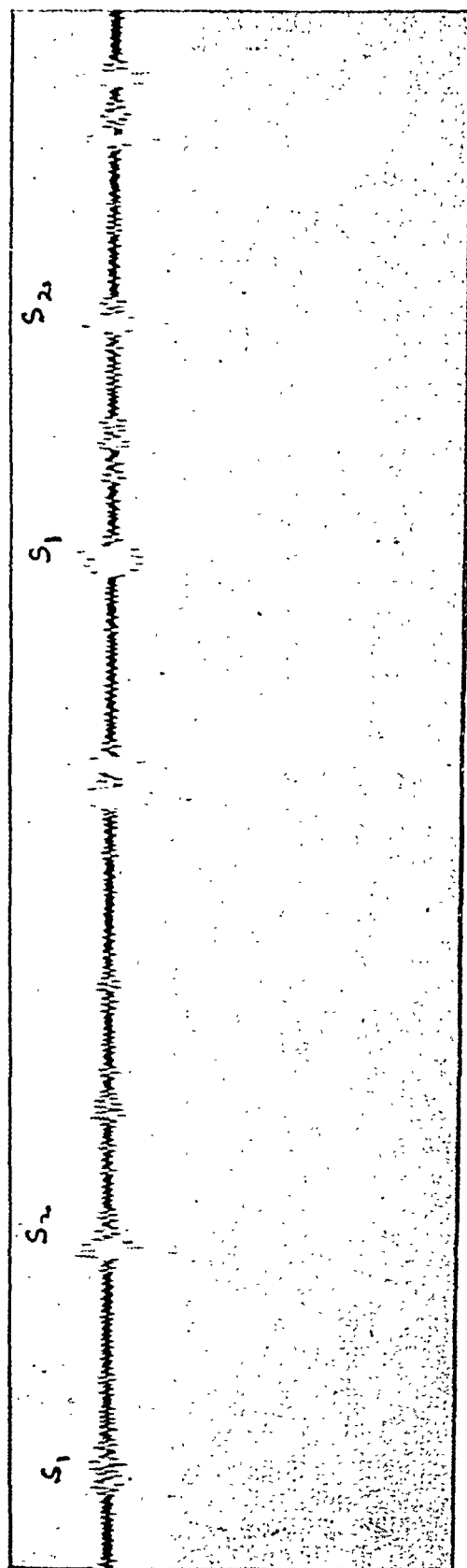


FIG. 2. Phonocardiogram in Case 3 demonstrating the sharpness of the crepitant sounds, and their occurrence during systole and diastole. S<sub>1</sub> and S<sub>2</sub> refer to the first and second heart sounds.

Nov. 15, 1944

LEAD

Jan. 8, 1945

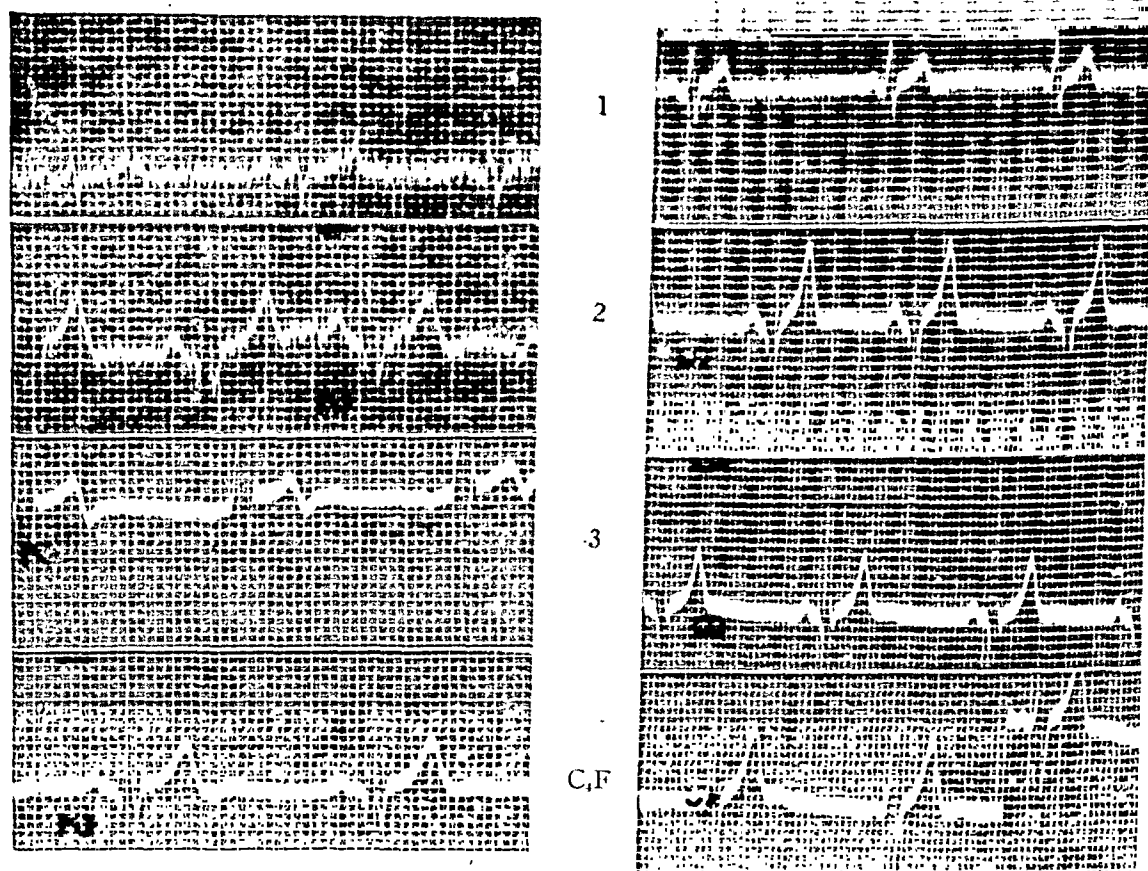


FIG. 3. Electrocardiograms in Case 3 demonstrating the slight shift in electrical axis. (The timer was out of order in the tracing taken January 8, 1945).

air under pressure through the catheter results in overinflation of the alveoli with the development of multiple minute ruptures in their walls which permit air to leak into the sheaths of the pulmonary blood vessels lying in intimate contact with the alveolar walls. The air dissects along the sheaths to the hilus, aided by the respiratory lengthening and shortening of the blood vessels, and may then enter the mediastinum. Occasionally, the air may dissect to the pleural surface, forming a subpleural bleb, which may rupture and cause a pneumothorax. As a result of the increased pressure due to accumulation of air in the interstitial tissue of the lung or mediastinum, escape outlets develop in experimental animals with consequent spread to the retroperitoneal tissues, the subcutaneous tissues of the body (principally of the neck and thorax), to the potential space between the parietal pleura and the pericardium, to the anterior mediastinum, and to the opposite lung. Similar escape mechanisms have developed in clinical instances of interstitial emphysema.

The frequent occurrence of pneumothorax in patients with mediastinal emphysema probably represents, in most instances, a mechanism whereby the

deleterious effects of increased mediastinal pressure are obviated. By analogy with the experimental animal, wherein the mediastinal wall may rupture as a result of the pneumomediastinum, it has been postulated that the increase in mediastinal pressure in patients with similar difficulties may result in pneumothorax via the same route, i.e., rupture of the mediastinal wall. The development of a pneumothorax with collapse of the lung, besides serving as a means for decreasing the mediastinal pressure, tends to stop the leakage of air from the alveoli. We have as yet no means of differentiating clinically those instances in which pneumothorax is due to rupture of a pleural air bleb, but it appears highly probable that either may occur.

The distention of the sheaths of the pulmonic blood vessels by the escaping air may result in interference with blood flow and circulatory embarrassment. The air which reaches the mediastinum may also lead to impaired circulatory efficiency by pressure on the heart and great vessels. In a study on the effects of increased mediastinal pressure in animals, Ballou and Francis<sup>6</sup> found that some of the consequences may be stagnation of blood in the lungs, impairment of heart action, pericardial effusion, and edema of the tracheobronchial mucosa. The development of a pneumothorax or subcutaneous emphysema helps prevent such dire effects by decreasing the tension in the mediastinum.

The cause of the initial alveolar ruptures in cases of interstitial pulmonary emphysema of so-called spontaneous origin is far less apparent than in instances such as develop during the violent expulsive efforts of parturition or following laryngeal fractures, tracheotomy or other surgical procedures at the base of the neck, trauma to the thorax, aspiration of foreign bodies, asthma, or infections such as influenza, lobar or bronchopneumonia and croup. Several cases<sup>7</sup> have been reported in infants, wherein congenital atelectasis is a significant factor. Macklin<sup>2</sup> has suggested that the origin of interstitial emphysema of the type described by Hamman may be in small areas of pulmonary alveolar hyperinflation (compensatory emphysema) associated with nearby atelectatic patches. This suggestion is logical, but awaits definite proof. In only one patient (No. 27) in the series tabulated here was suggestive evidence of atelectasis found. However, it is quite true that small areas of pulmonary atelectasis of obscure origin may exist without roentgenologic evidence, at least in the postero-anterior projections. Miller<sup>27</sup> recorded a case of mediastinal emphysema associated with massive post-tonsillectomy atelectasis of the right lung.

The fact that several of the patients gave histories of repeated episodes suggests another factor which may be of significance, and that is the possibility of a constitutional defect in the alveolar walls. In summary, then, our present conception of the pathogenesis of mediastinal emphysema of spontaneous origin is that air leaks from the alveoli (as a result of local compensatory emphysema and/or a constitutional defect) into the perivascular connective tissue, and thence to the hilus and the mediastinum.



## CLINICAL FEATURES

In addition to the three histories recorded here, we were able to find records of 36 other cases of spontaneous mediastinal emphysema in the literature,<sup>1, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27</sup> and we have collected the pertinent clinical features of these 39 case histories in the form of a table. We have omitted from consideration two patients reported by Scott<sup>28</sup> in whom the mediastinal emphysema developed after a half-mile foot race in one instance, and after a hundred-mile cycle race in another, a case recorded by Schwemlein<sup>29</sup> following an open ether anesthesia, and one reported by Greene<sup>22</sup> occurring during labor. These records were not included because spontaneity in onset was absent, although the clinical manifestations in those instances were similar to those in cases of so-called spontaneous origin. The case of Wolferth and Wood<sup>30</sup> which is referred to in many of the reports as an example of mediastinal emphysema, impressed us as probably an instance of "pericardial knock" occurring in a left-sided pneumothorax of spontaneous origin, and was, therefore, also excluded. Cases occurring in infants were excluded because of the close association with atelectasis.

## ETIOLOGY

1. *Age.* The average age of the 39 patients was 26.7 years, with a range of 15 to 52 years. Eight patients were under 21 years of age, and 22 patients were between 21 and 30 years. Only seven patients were more than 30 years old, indicating that spontaneous mediastinal emphysema is more likely to affect young adults.

2. *Sex.* In this collected series there are 36 males and three females. It is not clear why there should be such a high preponderance of males, particularly since the absence of definite exciting causes would rule out the factor of increased male exposure to accidents or occupational injuries.

3. *Color.* Two of the recorded instances occurred in Negroes; the others (where data are given) occurred in white people. In a series as small as this one, the distribution of color incidence has no significance except to indicate that spontaneous mediastinal emphysema may occur in either colored or white people.

4. *Occupation.* Analysis of the occupation of the 39 patients yields nothing of interest, except that seven of the patients were physicians or medical students. It is very unlikely that this relatively high incidence among medical men reflects any particular predilection for this profession. The severe chest pain characteristic of spontaneous mediastinal emphysema would cause apprehension in any of us, coronary-conscious as we are, and would stimulate us more readily than the less conditioned laity to seek advice from our colleagues.

5. *Contributory Factors.* In 16 instances, there were no contributory factors worthy of note. In 14 patients, the symptoms developed during,

or within a few hours after very mild to moderate physical exertion, such as walking, driving, light labor, golfing, volleyball, vomiting or playing a trombone. An antecedent or concurrent respiratory infection was considered of possible significance in seven instances. One case developed during diabetic ketosis and another during fever therapy. Thus, there is no one definite factor which can be incriminated as an excitant, although physical exertion and respiratory infections may be of significance as predisposing causes. Increased intrapulmonary tension such as might result from coughing or trombone playing or vomiting could conceivably precipitate alveolar rupture at points of weakness.

### SYMPTOMS

1. *Pain.* The sudden onset of pain in the chest is usually the first symptom in spontaneous interstitial emphysema of the lung or mediastinum. In only one case of the series (No. 11) was the development of pain gradual, and in only three cases (Nos. 16, 27 and 33) was pain absent entirely. The pain was usually described as sharp and stabbing or knife-like in character, but the intensity varied greatly from mild aching discomfort to excruciating distress. From the description given in the histories, we gathered that the pain at the onset was severe in more than half of the cases, frequently being of such intensity that myocardial infarction was suspected. The initial pain was located in the precordial area or the left anterior chest in 18 instances, retrosternally in six, in the left side or axilla in six, in the lower right chest in one, in the left chest posteriorly in three, and in the mid-scapular area in two.

As Macklin<sup>20</sup> has pointed out, it is possible in an occasional case to distinguish two successive types of pain, the first being a relatively mild sharp twinge in the lateral chest wall possibly due to the development of pulmonary interstitial (i.e., perivascular) emphysema following alveolar ruptures and consequent interference with pulmonary blood flow. After a few hours, during which time the extravasated air presumably migrates to the mediastinum, the second type of pain supervenes, recognizable by its greater intensity, its sharper character, and its more central location. It appears likely that this latter pain is due to the distention of the mediastinal tissues with air, although it has been suggested that interference with blood flow in the larger pulmonary vessels at the hilus may be responsible.

The radiation of the pain simulates that of angina pectoris, and the commonest direction of radiation is to the left shoulder and down the left arm. Occasionally the pain may radiate to the neck or to the back. It would seem logical to attribute the similarity of radiation in angina pectoris and mediastinal emphysema to transmission of the sensation via the same nerve pathways; however, Macklin<sup>20</sup> has suggested that the pressure of the air in the mediastinum may actually indent the coronary arteries, thus interfering with the blood supply of the heart. Scott<sup>28</sup> has suggested that this

anginal pain may be the result of stretching of the investment of the aorta, as Allbutt postulated for angina pectoris.

The pain may last from a few moments to several hours or days, and then gradually disappears. The severity and duration of the pain are undoubtedly dependent upon the degree of distention of the mediastinal tissues with air. If the amount of air entering the mediastinum is small, pain may be mild or absent. If the aberrant air increases in amount the discomfort mounts proportionately unless an escape mechanism is provided. The development of subcutaneous emphysema or a pneumothorax provides an outlet for the air and thus affords some relief to the compressed mediastinal structures.

In the majority of instances, the intensity of the pain was readily influenced by changes in the position of the patient. Recumbency, particularly in the left lateral position, aggravated the pain, whereas the erect posture afforded some relief. The basis for the variability of pain in relation to posture is obviously mechanical.

2. *Crackling Sensation.* With the onset of chest pain, or in a few hours to a few days thereafter, the patient may become conscious of a peculiar sensation in the retrosternal or precordial area, variously described as crackling or crunching or bubbling or grinding. This sensation is not a painful one, and is not necessarily synchronous with the pain due to mediastinal distention, but a few patients noticed that the sensation appeared to be related to the action of the heart. At least six patients were able to hear sounds of similar quality emanating from their chests. The sensation and the sounds were best appreciated in the left lateral position. This feature, which is the most characteristic clinical element in mediastinal emphysema, will be discussed in greater detail later.

3. *Dyspnea.* Increase in the respiratory rate with consciousness of respiratory difficulty occurred in 19 instances. As might be expected, dyspnea was more frequent and more pronounced when pneumothorax was associated (13 instances). Several patients exhibited pneumothorax without dyspnea. However, in six patients in whom pneumothorax was not demonstrated, dyspnea was present and was probably due to interference with pulmonary blood flow by the distention of the vessel sheaths with air. The dyspnea which occurs with spontaneous mediastinal emphysema is usually mild and is not associated with cyanosis or orthopnea.

4. *Other Symptoms.* Palpitation, dysphagia, pain during deep inspiration, and pain on turning the neck have been noted in occasional cases. Anxiety and profuse perspiration are common accompaniments at the onset. Minor complaints related to the mediastinal emphysema are relatively uncommon; the history is usually clear-cut, with chest pain, crackling sensation or sounds retrosternally, and possibly dyspnea. The diagnosis is frequently suggested simply by the history.

## PHYSICAL SIGNS

1. *Mediastinal Crepitation (Hamman's Sign)*. The most characteristic sign of mediastinal emphysema is an extraordinary crunching sound audible through the stethoscope over the cardiac area. This peculiar sound, which is unmistakable after having once been heard, was described by Hamman and frequently has been referred to as Hamman's sign; with all due respect to Hamman, the perpetuation of eponymic designations in medicine is undesirable, and the term *mediastinal crepitation* is a good descriptive phrase. Different students have characterized the sounds as crackling, clicking, bubbling, crunching, grinding, rasping or snapping, and have described the sounds as simulating the rattle of dried peas on a taut canvas, the crinkling of cellophane, the sounds of footsteps in packed snow on a dry brisk day, the squeaking of a leather saddle, the cooing of doves, or rubbing distended rubber balloons against each other. Such descriptive analogues, besides suggesting that poetry may be part of the art of medicine, aid in the recognition of these sounds.

The mediastinal crepitation is sensed by the patient (as previously described) and is frequently audible to the patient. Through the stethoscope the sounds are loud, and coarse, and seem to arise close to the anterior chest wall. They occur in the systolic and the diastolic phases of the cardiac cycle (as shown in the phonocardiogram, figure 2), usually being more marked during systole, and are due to the compression of air in the mediastinum by the movements of the heart. McGuire and Bean<sup>8</sup> have duplicated these sounds experimentally in dogs. The sounds are occasionally of sufficient volume to be audible with the unaided ear at a distance of several feet from the patient. The mediastinal crepitation is usually best heard when the patient is in the left lateral recumbent position, and is diminished by the erect posture or right lateral recumbency. During inspiration the sounds may not be as pronounced as in expiration.

The sounds are audible over a period varying from a few hours to six weeks or longer, with an average duration of about eight days. However, the sounds may not be present at all times during this period. It is important to keep in mind the variability of the crepitation with postural changes, and to listen particularly with the patient in the left lateral position.

In only one case in the series (No. 25) was this sign absent throughout the course of the illness. Macklin's experimental work indicates that the air enters the mediastinum via the lung roots and accumulates first in the middle and posterior mediastinal spaces, thence spreading forward between the parietal pleura and parietal pericardium to the anterior mediastinum ("pneumoprecordium"). Thus, in an occasional case wherein the leakage is not great, the anterior mediastinum may not be infiltrated with air, and the crepitant sounds dependent upon the heart action may not be heard.

The sound of mediastinal crepitation must be differentiated from the "pericardial knock" which is heard occasionally in left-sided pneumothorax

of spontaneous<sup>31</sup> or traumatic origin. The "pericardial knock" was described during the war of 1914-1918<sup>32</sup> in gunshot wounds of the chest, and is a loud, sharp, hollow, knocking or clicking sound, systolic in time, usually loudest during inspiration, and readily distinguished from the more continuous, crunching, systolic and diastolic sounds heard in mediastinal emphysema. It seems clear that the mediastinal crepitation is due to the presence of emphysematous blebs near the heart which are disturbed by the heart's action. The origin of "pericardial knock" is not as clear, however, and several theories have been proposed: Lister<sup>31</sup> suggested that the sound may arise in the left pulmonary artery when it is partially obstructed at the hilus by the collapse and displacement of the left lung, in a manner analogous to the production of the sounds heard when determining the blood pressure. Scadding and Wood<sup>33</sup> suggested that the sound may be due to the forcible separation of the visceral and parietal pleura during cardiac contraction, when the air in the pleural space is so distributed that it can be moved by the cardiac pulsations. Greene<sup>22</sup> agrees that the sound is due to the heart striking an air bubble, but suggests that the air may be an emphysematous bleb on the medial aspect of a collapsed left lung or a gas bubble in the splenic flexure of the colon.

2. *Decreased Cardiac Dullness.* Diminution of the area of cardiac dullness, or replacement of cardiac dullness by hyperresonance is an expected concomitant of pneumomediastinum. However, in only 12 cases in the series was mention made of such findings. In eight instances, the decreased cardiac dullness was associated with a concurrent left pneumothorax, and in four instances there was no such association.

3. *Pneumothorax.* In 21 of the recorded cases of spontaneous mediastinal emphysema a pneumothorax on the left side was found, usually small in degree. An occasional case (such as our third one) exemplified the development of a pneumothorax after mediastinal emphysema had developed, but in the majority of instances, the pneumothorax and pneumomediastinum were discovered simultaneously. In studying the case reports, it seemed to us that those patients with most severe pain were likely to have an associated pneumothorax, and this impression would tend to substantiate the conception previously described that pneumothorax acts as a relief vent for the increased intramediastinal pressure. Of suggestive significance, also, is the fact that none of the three patients in whom pain was absent exhibited pneumothorax. However, the evaluation of the chest pain is subject to too many subjective influences to warrant its use as an accurate index. There was no correlation between the presence or absence of pneumothorax and the duration of mediastinal crepitation, the latter averaging about eight days in both groups.

Of Hamman's seven cases<sup>1</sup> two exhibited pneumothorax on the left side, and Hamman saw no reason other than accident why it should not involve the right side. Yet all the recorded instances of pneumothorax in association with spontaneous mediastinal emphysema involve only the left side

Perhaps this predilection is due to the slapping action of the heart against the left side of the pericardium during the diastolic fling of the heart, since the right side of the heart is anchored by the venae cavae.

4. *Subcutaneous Emphysema.* The development of subcutaneous emphysema is another mechanism by which intramediastinal tension is relieved. In eight cases in this series, distention of the subcutaneous tissues was found, usually involving the neck, supraclavicular spaces, or anterior thoracic wall. An associated pneumothorax was found in two of these eight cases, whereas the other six had no pneumothorax, indicating perhaps that the development of the subcutaneous emphysema obviated, in some cases, the necessity for further relief of tension via rupture of the mediastinal wall. In Adcock's case (No. 17), the air spread to the neck, chest, abdomen, genitalia, perirectal tissues, and lower extremities, but this is an unusually extensive spread. One patient (No. 21) developed retroperitoneal emphysema without subcutaneous emphysema.

5. *Respiratory Rate.* The respiratory rate was increased to 20 or more per minute in 19 cases. The tachypnea is usually of mild degree, and, as has been mentioned, is not accompanied by cyanosis or orthopnea.

6. *Temperature, Pulse Rate, and Blood Pressure.* Fever is uncommon in spontaneous mediastinal emphysema. Of the three cases in this series which exhibited definite transient elevation of the temperature beyond 99.6° F., one (No. 6) was in diabetic ketosis, and one was receiving fever therapy for syphilis (No. 27), leaving only one case (No. 2) in which the fever could be attributed to the pneumomediastinum.

Transient acceleration of the pulse above 90 beats per minutes was observed in only four instances, one of which was the patient in diabetic ketosis (No. 6). Thus, tachycardia is uncommon in this clinical picture.

The blood pressure was within normal limits in all cases, again excepting the patient in ketosis (blood pressure 90 mm. Hg systolic and 60 mm. diastolic).

9. *Other Signs.* Hyperesthesia of the skin in the area of chest pain was observed in only one instance (No. 25).

#### LABORATORY FINDINGS

1. *Roentgenographic Evidence of Air in the Mediastinum.* Air along the cardiac borders or in the anterior mediastinum was visible in the roentgenogram, or fluoroscopically, in 14 cases. Probably if oblique and lateral views had been taken more often the percentage would be greater. It most often appears as a narrow band of decreased density along right border (or both) of the mediastinal shadow in the anterior projection. Bubbles of air may be seen in the anterior or posterior mediastinum in the lateral projections. In Kellogg's case (No. 25), crepitation was absent, and the diagnosis was established by the roentgenographic findings.

| Author and Ref.                | No. | Age | Sex | Col. | Occupation      | Contributory Factors  | Pain              |                      |                               | Duration of Sign | Pneumo-thorax | Subcutaneous Emphysema | Roentgen-Ray Evidence of Pneumo-mediastinum | Resp. Rate | Pulse Rate | Blood Pressure | Temp.           | WBC    | EKG                       | Comment                                                                                                                                       |
|--------------------------------|-----|-----|-----|------|-----------------|-----------------------|-------------------|----------------------|-------------------------------|------------------|---------------|------------------------|---------------------------------------------|------------|------------|----------------|-----------------|--------|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
|                                |     |     |     |      |                 |                       | Location          | Intensity            | Radiation                     |                  |               |                        |                                             |            |            |                |                 |        |                           |                                                                                                                                               |
| Hamman <sup>1</sup>            | 1   | 51  | M   | W    | Physician       | None                  | Substernal        | Severe               | L. shoulder                   | "Few days"       | None          | None                   | No                                          | 20         | 54         | 110/80         | Norm.           | Norm.  | Low volt.                 | Possible bronchiectasis, right base.                                                                                                          |
|                                | 2   | 17  | M   | W    | Tin-worker      | None                  | Substernal        | Severe               | Neck                          | —                | None          | Neck, supra-clavicular | Yes                                         | 24         | 86         | 110/70         | 101.2           | 13,000 | —                         | Fever was transient.                                                                                                                          |
|                                | 3   | 25  | M   | W    | Physician       | Respiratory infection | Precordial        | "Rather sharp"       | L. side, chest                | 8 days           | None          | None                   | No                                          | —          | —          | —              | 99.4            | Norm.  | —                         |                                                                                                                                               |
|                                | 4   | 34  | M   | W    | —               | Long drive            | Substernal        | Very severe          | Shoulders, L. arm             | 2 days           | Left          | None                   | No                                          | —          | Norm.      | —              | Norm.           | Norm.  | Low volt. Lead I          | Small areas of apical infiltration found later. Within next few years, developed spont. pneumothorax twice on left, and three times on right. |
|                                | 5   | 29  | M   | W    | Salesman        | None                  | Lower L. Chest    | Severe               | —                             | —                | Left          | None                   | No                                          | —          | —          | —              | —               | —      | —                         |                                                                                                                                               |
|                                | 6   | 16  | M   | W    | —               | Diabetic ketosis      | Lower R. chest    | Severe               | —                             | —                | None          | Neck, supra-clavicular | Yes                                         | 35         | 120        | 90/60          | Elevated 2 das. | 28,500 | —                         | WBC was normal by next day.                                                                                                                   |
|                                | 7   | 25  | M   | W    | Physician       | None                  | Lower L. axilla   | Moderate             | Precordium, L. shoulder, neck | "Few days"       | None          | None                   | No                                          | Norm.      | Norm.      | Norm.          | Norm.           | Norm.  | Slight rt. axis deviation |                                                                                                                                               |
| McGuire and Beane <sup>2</sup> | 8   | 17  | F   | W    | —               | Dribbling Basketball  | L. anterior chest | Moderate             | —                             | 6 days           | Left          | Over sternum           | Yes (Lateral)                               | 20         | 96         | 130/80         | 99.0            | 11,000 | Norm.                     |                                                                                                                                               |
| Morey and Sosman <sup>3</sup>  | 9   | —   | M   | W    | Medical Student | None                  | Precordium        | Severe               | L. shoulder L. arm            | 2 weeks          | Left          | None                   | Yes                                         | Norm.      | Norm.      | Norm.          | 97.2            | —      | Slight rt. axis dev.      | Similar episode six weeks later.                                                                                                              |
| Wolff <sup>4</sup>             | 10  | 27  | M   | —    | Laborer         | Mild manual labor     | L. side chest     | "Sharp" "knife-like" | —                             | 3 weeks          | Left          | None                   | Yes (fluoroscopic)                          | Incr.      | —          | 130/80         | 98.6            | Norm.  | —                         |                                                                                                                                               |
| Matthews <sup>5</sup>          | 11  | 25  | M   | C    | Laborer         | Respiratory infection | L. ant. chest     | Gradual in onset     | —                             | 12 days plus     | Left          | None                   | No                                          | Incr.      | Norm.      | Norm.          | Norm.           | —      | —                         |                                                                                                                                               |
| Pinkney <sup>6</sup>           | 12  | 25  | F   | —    | —               | None                  | Chest             | Moderate (?)         | —                             | —                | Left          | None                   | No                                          | Incr.      | —          | —              | —               | —      | —                         | Two previous and three subsequent episodes of spont. pneumothorax.                                                                            |
|                                | 13  | 25  | M   | —    | —               | None                  | L. post. chest    | Severe               | —                             | 1 day            | None          | None                   | No                                          | —          | —          | —              | —               | —      | —                         |                                                                                                                                               |

| Author and Ref.               | No. | Age | Sex | Col. | Occupation         | Contributory Factors | Pain                             |                    |                                 | Duration of Sign | Pneumo-thorax | Subcutaneous Emphysema | Roentgen-Ray Evidence of Pneumo-mediastinum | Resp. Rate | Pulse Rate | Blood Pressure | Temp. | WBC   | EKG                | Comment                                                                          |
|-------------------------------|-----|-----|-----|------|--------------------|----------------------|----------------------------------|--------------------|---------------------------------|------------------|---------------|------------------------|---------------------------------------------|------------|------------|----------------|-------|-------|--------------------|----------------------------------------------------------------------------------|
|                               |     |     |     |      |                    |                      | Location                         | Intensity          | Radiation                       |                  |               |                        |                                             |            |            |                |       |       |                    |                                                                                  |
| Skyron <sup>13</sup>          | 14  | 33  | M   | —    | —                  | Walking (?)          | Mid-scapular                     | "Gripping"         | Precordium, L. shoulder, L. arm | Few hrs.         | None          | None                   | No                                          | 22         | 65         | 110/80         | 97.8  | Norm. | Norm.              | Similar attack twelve years previously.                                          |
|                               | 15  | 22  | M   | —    | —                  | Walking (?)          | Precordial and lt. side of chest | "Stabbing"         | —                               | 12 hours         | Left          | None                   | No                                          | 20         | 70         | 120/80         | 98    | —     | Norm.              |                                                                                  |
| Caldwell <sup>14</sup>        | 16  | —   | M   | —    | Lawyer             | Coughing             | No pain                          |                    |                                 | 1 week           | None          | None                   | No                                          | Norm.      | 80         | 124/74         | 99    | Norm. | Norm.              |                                                                                  |
| Miller <sup>15</sup>          | 17  | 27  | M   | W    | Physician          | Walking (?)          | L. upper back                    | "Exercising"       | L. shoulder, arm                | 1 week           | Left          | None                   | No                                          | 22         | 80         | 125/75         | 98.4  | —     | —                  |                                                                                  |
|                               | 18  | 23  | M   | W    | Student            | Walking (?)          | L. costal margin and pre-cordium | Severe             | L. shoulder, arm                | 10 days          | Left          | None                   | Yes                                         | 20         | 80         | 110/55         | 97.6  | —     | —                  |                                                                                  |
| Murphy and Zeis <sup>16</sup> | 19  | 15  | M   | W    | Student            | "Head cold"          | Neck and retrosternally          | "Sharp"            | —                               | 4 days           | None          | Neck                   | Yes                                         | 18         | 84         | 120/70         | 98.4  | Norm. | —                  |                                                                                  |
| Griffin <sup>17</sup>         | 20  | 30  | M   | W    | Student            | None                 | Chest                            | "Vague discomfort" | —                               | —                | Left          | None                   | No                                          | —          | —          | —              | —     | —     | Norm.              |                                                                                  |
|                               | 21  | 18  | M   | W    | Student            | None                 | Precordial                       | Moderate           | —                               | 6 days           | Left          | None                   | No                                          | Incr.      | —          | —              | —     | —     | —                  | Developed retro-peritoneal emphysema.                                            |
|                               | 22  | 20  | M   | W    | Student            | Light work           | L. side of chest                 | —                  | —                               | 8 days           | Left          | None                   | No                                          | —          | —          | —              | —     | —     | —                  | Probably had two previous episodes.                                              |
|                               | 23  | 18  | M   | W    | Student            | Playing trombone     | L. side of chest                 | "Sharp"            | —                               | —                | Left          | None                   | No                                          | —          | —          | —              | —     | —     | —                  |                                                                                  |
| Meek <sup>18</sup>            | 24  | 27  | M   | —    | Auto Supply Worker | None                 | L. of lower sternum              | "Severe soreness"  | L. scapula                      | 6 weeks          | None          | None                   | Yes (Fluoroscopic)                          | Norm.      | 72         | 120/80         | Norm. | Norm. | —                  | Kline + plus.                                                                    |
| Kellogg <sup>19</sup>         | 25  | 22  | M   | W    | No                 | None                 | L. border of heart               | Severe             | —                               | Absent           | None          | L. Supra-clav.         | Yes                                         | —          | Norm.      | —              | —     | —     | Norm.              | Typical sounds were not present at any time. Hyp-peresthesia along area of pain. |
| Dassen and Fong <sup>20</sup> | 26  | 23  | F   | —    | —                  | None                 | Precordial                       | Severe             | L. shoulder, arm                | 5 days           | Left          | None                   | Yes                                         | 35         | 90-100     | 120/70         | Norm. | 8,200 | Low voltage Lead I | Four similar episodes within a few weeks, and recurrence the next yr.            |



| Author and Ref.               | No. | Age | Sex | Col. | Occupation         | Contributory Factors                | Pain                             |           |                            | Duration of Sign | Pneumo-thorax | Subcutaneous Emphysema                                | Roentgen-Ray Evidence of Pneumo-mediastinum | Resp. Rate | Pulse Rate | Blood Pressure | Temp. | WBC    | EKG                  | Comment                                                              |
|-------------------------------|-----|-----|-----|------|--------------------|-------------------------------------|----------------------------------|-----------|----------------------------|------------------|---------------|-------------------------------------------------------|---------------------------------------------|------------|------------|----------------|-------|--------|----------------------|----------------------------------------------------------------------|
|                               |     |     |     |      |                    |                                     | Location                         | Intensity | Radiation                  |                  |               |                                                       |                                             |            |            |                |       |        |                      |                                                                      |
| Adcock <sup>21</sup>          | 27  | 52  | M   | W    |                    | Fever therapy for tertiary syphilis | No pain                          |           |                            | 8 days           | None          | Neck, chest, abdomen, perigenital, perirectal, thighs | Yes                                         | Norm.      | —          | —              | 100.6 | —      | —                    | ? small area of atelectasis at left base.                            |
| Greene <sup>22</sup>          | 28  | 41  | M   | C    | Physician          | None                                | Substernal                       | Severe    | L. shoulder                | 10 days          | None          | None                                                  | Yes (Oblique)                               | —          | Norm.      | —              | Norm. | —      | —                    |                                                                      |
| Linza <sup>23</sup>           | 29  | 22  | M   | W    | Mechanic           | None                                | L. side of chest                 | Severe    | Back                       | 2 days           | Left          | Lower chest                                           | No                                          | 18         | 90         | 130/82         | 99.4  | 19,500 | —                    |                                                                      |
| Monroe and Webb <sup>24</sup> | 30  | 21  | M   | —    | Soldier            | None                                | Pre-cordium                      | Moderate  | None                       | 3 days           | None          | None                                                  | No                                          | Norm.      | 80         | 145.85         | Norm. | —      | Norm.                | Similar episodes eight months previously and two weeks subsequently. |
| Hoffman et al. <sup>25</sup>  | 31  | 28  | M   | W    | Ambulance Employee | Lifting patient                     | Substernal                       | Severe    | L. Arm                     | 4 days           | Left          | None                                                  | No                                          | 30         | 90         | 130/90         | Norm. | Norm.  | Low voltage          | Phonocardiogram recorded.                                            |
| Israel <sup>26</sup>          | 32  | 51  | M   | —    | Painter            | Respiratory infection               | No pain                          | —         | —                          | 7 days           | None          | None                                                  | No                                          | 20         | —          | 150/90         | Norm. | —      | Norm.                |                                                                      |
| Miller <sup>27</sup>          | 33  | 23  | M   | W    | —                  | Two rounds of golf                  | L. ant. chest                    | Mild      | None                       | 5 days           | None          | None                                                  | No                                          | Norm.      | 80         | 126/78         | Norm. | Norm.  | Norm.                |                                                                      |
|                               | 34  | 21  | M   | W    |                    | Vomiting, due alcohol               | L. costal margin and epigastrium | "Sharp"   | None                       | 6 days           | None          | Supra-clavicular                                      | No                                          | Incr.      | 88         | 132/80         | 99.2  | Norm.  | Left ax. shift       | Palpitation at onset.                                                |
|                               | 35  | 28  | M   | W    | Officer            | Respiratory infection (?)           | L. Scapula                       | "Sharp"   | L. shoulder, L. side chest | 6 days           | Left          | None                                                  | No                                          | Incr.      | 68         | 120/68         | Norm. | 16,040 | —                    |                                                                      |
|                               | 36  | 23  | M   | W    | Soldier            | Respiratory infection               | L. Ant. Chest                    | "Sharp"   | L. Supra-clav. area        | 15 days          | Left          | None                                                  | Yes                                         | Incr.      | 72         | 136/80         | Norm. | Norm.  | Norm.                |                                                                      |
| Fagin and Schwab              | 37  | 24  | M   | W    | Seaman             | Driving                             | Precordial                       | Severe    | Entire L. ant. chest       | 1 day plus       | Left          | None                                                  | No                                          | Incr.      | 100        | 104/82         | Norm. | Norm.  | —                    |                                                                      |
|                               | 38  | 38  | M   | W    | Musician           | None                                | Interscapular and substernal     | Severe    | Neck                       | Few hrs.         | None          | None                                                  | No                                          | Norm.      | 84         | 130/80         | 99.2  | Norm.  | Norm.                |                                                                      |
|                               | 39  | 20  | M   | W    | Medical Student    | Two hrs. after volley ball game     | Precordial                       | Moderate  | L. shoulder                | 5 days           | Left          | None                                                  | Yes                                         | Norm.      | 76         | 98/72          | Norm. | Norm.  | Slight shift in axis | Two previous similar episodes                                        |

2. *Leukocytosis.* Elevation of the white blood cell count is uncommon here and was noted in only five patients, including the one in ketosis. The erythrocyte sedimentation rate is usually also within normal limits.

3. *Electrocardiographic Changes.* Electrocardiograms are recorded in 19 of these cases, but only eight exhibited significant abnormalities. Low voltage, particularly in Lead I, occurred in four patients, and changes in the electrical axis in four others, probably as a result of the dampening and displacing effect of the air in the mediastinum. Phonocardiographs are recorded from the patient of Hoffman et al. (No. 31) and from one of our patients, and illustrate the sharpness of the crepitant sounds, and their relation to the cardiac cycle.

### DIFFERENTIAL DIAGNOSIS

It is apparent that almost any disease entity which is characterized by pain in the chest may enter into the differential diagnosis of spontaneous mediastinal emphysema. Myocardial infarction or insufficiency, pericarditis, dissecting aortic aneurysm, pleurisy, pulmonary embolism, and intercostal neuritis are of particular significance. The diagnosis of uncomplicated spontaneous interstitial emphysema limited to the lung is difficult because the signs are equivocal and roentgenograms are seldom helpful; however, since it is likely that most instances of spontaneous pulmonary interstitial emphysema of any significant degree are complicated by pneumomediastinum or pneumothorax or both, perhaps the differentiation is of little value. Intercostal neuritis may be distinguished by the distribution of pain and sensory findings, and the absence of mediastinal crepitation and other features of mediastinal emphysema.

Myocardial infarction and other serious diseases of the thoracic viscera can be readily differentiated from spontaneous mediastinal emphysema if it is remembered that the latter is distinguished by the following features: (1) Occurrence in young adults primarily. (2) Absence of shock, fever, tachycardia, hypotension, leukocytosis, acceleration of the sedimentation rate, and significant electrocardiographic changes (other than low voltage or slight changes in electrical axis). (3) Presence of mediastinal crepitation, diminished cardiac dullness, frequent association of subcutaneous emphysema or pneumothorax, and roentgenographic evidence of mediastinal air.

### PROGNOSIS

In all the recorded cases of spontaneous mediastinal emphysema occurring after infancy the course was benign and recovery occurred within a few days to a few weeks. Fisher<sup>34</sup> suggests that the more serious prognosis which this condition carries in infancy may be due to the poorly developed musculature of the pulmonary blood vessels and the atria of the heart, rendering these structures more collapsible in the very young. The possible consequences of increased mediastinal tension that have been de-

scribed by Ballou and Francis,<sup>6</sup> such as pulmonary edema or congestion and pericardial effusion, have not occurred in the cases we have reviewed.

Two of the patients in the recorded series (Nos. 3 and 12) had repeated episodes of spontaneous pneumothorax, and six patients (Nos. 9, 14, 22, 26, 30, 38) had repeated attacks of mediastinal emphysema. The patient described by Dassen and Fongi<sup>20a</sup> had four attacks within a few weeks, and Fongi<sup>20b</sup> described another episode in the same patient one year later, suggesting that a persistent pneumomediastinal fistula (between the ruptured alveoli and the mediastinum) might be responsible. However, the possibility of an underlying constitutional defect is more likely.

### TREATMENT

Reassurance is the most beneficial treatment in the majority of patients with spontaneous mediastinal emphysema. Analgesics may be necessary to control the pain at the onset, and it is probably advisable for these patients to be at rest until the symptoms begin to abate. Symptomatic measures have been successful in all these cases, but it is conceivable that a patient may be encountered in whom it might be necessary to induce a pneumothorax to stop the escape of air from the lung into the perivascular tissues, or in whom incisions may be necessary to allow escape of air trapped in the mediastinum.

### SUMMARY

1. Three new cases of spontaneous mediastinal emphysema are reported, and the clinical features of this syndrome are reviewed by analyzing all the recorded cases.
2. The present conception of the pathogenesis of mediastinal emphysema is presented briefly.
3. The prominent diagnostic features are anterior chest pain, mediastinal crepitation, diminished cardiac dullness, frequent occurrence of pneumothorax or subcutaneous emphysema, roentgenographic evidence of mediastinal air, and the absence of shock, fever, leukocytosis, accelerated sedimentation rate, or significant electrocardiographic changes.
4. All the cases reported beyond infancy have been characterized by a benign course, and a satisfactory response to symptomatic treatment. Recurrences are not uncommon and the syndrome may be due to an underlying constitutional defect.

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*Addendum:* Since this paper was completed, we have noted two additional articles dealing with the subject:

1. MACKLIN, M. T., and MACKLIN, C. C.: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment, *Medicine*, 1944, xxiii, 281-358.
2. HAMMAN, L.: Mediastinal emphysema, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1-6. Dr. Hamman herein reports another case of spontaneous mediastinal emphysema, the patient being a 26 year old male. The clinical features were similar to those described in the foregoing discussion, but the electrocardiograph revealed inverted T-waves in the limb leads.

# CASE REPORTS

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## HISTOPLASMOSIS OF DARLING: REVIEW AND CASE REPORT WITH AUTOPSY \*

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HISTOPLASMOSIS is an acute, subacute or chronic; localized or systemic; sporadic, granulomatous, infectious, fatal disease, caused by the fungus, *Histoplasma capsulatum*. It is spreading quite rapidly or being recognized more frequently, or both.

In 1906, Richard P. Strong<sup>1</sup> published a paper on the etiology of some tropical ulcerations of the skin. He found in material curetted from a skin lesion, oval bodies, which resembled cockleshells, with a sharp outline, measuring about three to four micra in diameter; many of them contained particles of chromatin. They were found in large numbers, both free and enclosed in phagocytic endothelioid cells. He wrote, "They are, I believe, forms of blastomyces (torulae) though they are very different from the usual species of blastomyces encountered in certain human skin affections . . . the torulae have somewhat the appearance of the forms which have been described in certain cases of oriental boil or sore as species of protozoa related to the Donovan-Leishman bodies."

Strong refers to the "discovery by J. Homer Wright in 1903, in a case of Delhi boil, of certain bodies which have considerable resemblance to the organisms already described by Leishman and Donovan in cases of tropical splenomegaly." He also mentions Riehl (1886), Cunningham (1885) and others who described organisms in skin lesions which had a capsule or cuticle and which were present in endothelioid cells. It is possible that some of these early workers were observing the organisms of histoplasmosis. According to Parsons and Zarafonitis,<sup>69</sup> Strong is now of the opinion that his case was one of those rare infections of man by the fungus *Cryptococcus farciminosus*, the cause of epizootic farcy of horses.

In 1906, Samuel T. Darling,<sup>2</sup> pathologist at the Ancon Hospital, Canal Zone, published the first of his series of papers, "A Protozoön General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymph Nodes." In his subsequent papers, Darling named the organism *Histoplasma capsulatum* and the disease, Histoplasmosis. Although a misnomer, the term has become entrenched through custom and persists to the present time. DeMonbreun<sup>3</sup> suggested the name "cytomycosis" and Humphrey<sup>4</sup> added the adjective "reticuloendothelial." The name *reticuloendothelial cytomycosis* has not received general recognition and use.

Darling presented a good description of the organisms as they occur in tissues. He discovered them in the course of a systematic search for kala-azar,

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following the statement in 1905 of Sir Patric Manson that kala-azar or some analogous disease might be found in America. He was the first to recognize the systemic nature of the disease and he presented detailed descriptions of the pathologic changes in the various tissues of his three autopsied cases (two Martinique negroes and one Chinaman, all residents of the Canal Zone). He was the first fully to describe and clearly recognize the disease as a new entity.

In 1912 and 1913, daRocha-Lima<sup>5</sup> called attention to the similarity between *Histoplasma capsulatum* and *Cryptococcus farciminosus*, the cause of epizootic lymphangitis in horses. He concluded that *Histoplasma capsulatum* was a fungus. Meleney<sup>6</sup> reported that Darling concurred in the opinion of daRocha-Lima, that the organism was a fungus and not a protozoön.

Darling proved to be a prophet as well as a scientist. In 1907 he read a paper on Histoplasmosis at the College of Physicians and Surgeons in Baltimore. In closing his paper he made the statement that histoplasmosis was bound to appear in Baltimore some day. According to Meleney<sup>6</sup> Darling was killed in a motor accident in Syria on May 20, 1925.

For 15 years, no further cases of histoplasmosis were reported. In 1924 Riehl<sup>7</sup> in Vienna, reported granulomatous lesions in a white man. The lesions were present for seven years and were caused by budding fungus forms. The patient was treated with an arsenical but died with systemic involvement and characteristic signs and symptoms. Riehl did not diagnose his case but his photomicrographs are those of histoplasmosis.

In 1925 histoplasmosis was rediscovered, in Minnesota, by Watson and Riley.<sup>8</sup> They published their work in 1926 and 1928. Their case had splenomegaly and terminal pulmonary infection.

In 1926 Phelps and Mallory<sup>9</sup> reported a case from one of the United Fruit Company hospitals in Honduras. The organisms were found at autopsy in the lungs of a native who also had carcinoma of the liver.

Wade<sup>10</sup> reported a case to the Culion Medical Society in 1926. The lesions were chiefly pulmonary with ulcers of the nasal mucosa. His paper, "A Case of Systemic Mycosis Due to a Fungus of Uncertain Classification" described the organisms and lesions typical of histoplasmosis.

Crumrine and Kessel<sup>11</sup> in 1931 reported a case with severe gastrointestinal and generalized involvement.

In 1932 Müller<sup>12</sup> reported a case of histoplasmosis in a seven-year old Javanese boy who died with fever, emaciation and lymph node enlargement.

In 1933 and 1934, Hansmann and Schenken<sup>13</sup> reported a case with chronic ulcerative skin lesions. At autopsy there were found ulcers of the mouth, caseated areas in the adrenal glands and lesions in the lungs and lymph glands.

The etiology of histoplasmosis was better understood after Dodd and Tompkins<sup>14</sup> reported their case in 1934. The case was that of a six-month old infant with anemia and splenomegaly. Katherine Tompkins discovered the organisms in the monocytes of the peripheral blood, thus diagnosing the first living case. Positive blood cultures were obtained before death and at post mortem by De-Monbreun.<sup>3</sup> He demonstrated that the fungus was not *Cryptococcus farciminosus* and he reproduced the disease in monkeys, dogs and mice by inoculation of cultures.

Following this, no cases appeared in the literature until 1938 when the incidence of reports increased rapidly. They continue to appear in increasing

numbers up to the present time. The recent occurrence of two cases in Pennsylvania and one in New York State would seem to indicate that the disease is spreading northward and into the more populous areas of the eastern states.

Negroni,<sup>15</sup> in 1938, published a short report of the first Argentine case. In 1940, he reported a second case. Balina, Negroni, Bosq and Herrera<sup>16</sup> also reported one of these cases in detail together with a third case.

Agress and Gray<sup>17</sup> published a report of a seven-month old boy with a mucopurulent rhinitis, an ulcer in the mouth and generalized infection.

Amolsch and Wax<sup>18</sup> reported an eight-month old white girl having otitis media due to histoplasmosis.

Shaffer, Shaul and Mitchell<sup>19</sup> had an autopsied case of an 11-month old white girl with generalized histoplasmosis. The case was first diagnosed as one of aleukemic leukemia.

deAlmeida and deSilva Lacaz<sup>20</sup> isolated *Histoplasma capsulatum* from a case having skin lesions.

Clemens and Barnes<sup>21</sup> reported a case of a 33-year old negress, a "stemmer" in a tobacco factory. The disease was systemic and the organism was obtained from the spleen and blood.

Reid, Scherer and Irving<sup>22</sup> reported the case of a 38-year old negro who had diarrhea, hoarseness and cough. The lesions were found to be generalized.

Gunter and Lafferty<sup>23</sup> reported a case of a 54-year old white woman with a generalized infection by *Histoplasma capsulatum* which resembled undulant fever.

Williams and Cromartie<sup>24</sup> presented the case of a 56-year old white man with lymph node and pharyngeal infection.

Humphrey<sup>4</sup> published two interesting cases. In one, he found mycelial elements in a lung lesion in addition to the usual round or oval fungus forms.

Meleney<sup>6</sup> in 1940 published the first comprehensive review of the disease and listed 32 cases. The cases have now, five years later, increased to at least 79. Meleney presented two cases of his own which he described in greater detail in 1941. Some of the cases which he listed have been published subsequently by other authors.

Several review articles have appeared in the journals. The most comprehensive are those of Humphrey,<sup>4</sup> Meleney,<sup>6</sup> Boltjes,<sup>25</sup> Moore and Jorstad.<sup>26</sup> The latter is especially concerned with those cases showing lesions of the ear, nose and throat and with the mycology. The most recent review is that of Parsons and Zarafonitis with a report of seven cases.<sup>69</sup>

Some cases of histoplasmosis have been reported twice and many have been cited briefly in reviews prior to publication by the discoverer. This overlapping has given a false impression of the number of cases.

The epidemiology of histoplasmosis is essentially the history of the disease. Although the number of cases is small from a public health standpoint, the disease seems to be spreading, especially in the United States. In view of the fact that it is also highly lethal it seems necessary for the medical profession to be on the alert for further cases. It would also seem advisable to make the disease a reportable one. Histoplasmosis has been found rather widely distributed in the United States and occasional cases have been found elsewhere as can be seen from tables 1 and 2. Some authors, notably Meleney,<sup>6</sup> believe that the increase in the number of reported cases is due primarily to an increased awareness of the disease.



When one considers the distribution of the reported cases, they appear to be sporadic, so the present evidence would not indicate that the disease is epidemic.

The case in London of Derry et al.<sup>27</sup> was that of a soldier evacuated from a base hospital in France. The soldier had formerly been in India and the Sudan.

The etiological agent of histoplasmosis was first identified as a fungus by De-Monbreun.<sup>3</sup> Moore<sup>28</sup> studied the taxonomy of the organism. He placed it among the Coccidioideaceae (*Posadasia pyriformis* and *Posadasia capsulata*). It is said to be closely related to *Rhinosporidium seeberi*, and a member of the fungi imperfecti. Conant<sup>29</sup> who made a cultural study of the life-cycle believes that it belongs among the Moniliaceae.

Hansmann and Schenken<sup>13</sup> obtained the organism from a 43-year old white man who had thick, hard, red and scaly skin nodules for 16 years. These authors also established the fungus nature of the organism and reproduced the disease in the cat and dog. They classified the fungus in the genus *Sepedonium*.

TABLE I  
Cases of Histoplasmosis

| Authors and References *                                 | Locale                | Reported |
|----------------------------------------------------------|-----------------------|----------|
| 1. Darling No. 1 <sup>2</sup> . . . . .                  | Ancon, C. Z. . . . .  | 1906     |
| 2. Darling No. 2 <sup>2</sup> . . . . .                  | Ancon, C. Z. . . . .  | 1907     |
| 3. Darling No. 3 <sup>2</sup> . . . . .                  | Ancon, C. Z. . . . .  | 1907     |
| 4. Riehl <sup>7</sup> . . . . .                          | Austria . . . . .     | 1924     |
| 5. Watson, Riley <sup>8</sup> . . . . .                  | Minnesota . . . . .   | 1926     |
| 6. Phelps, Mallory <sup>9</sup> . . . . .                | Honduras . . . . .    | 1926     |
| 7. Wade <sup>10</sup> . . . . .                          | Philippines . . . . . | 1926     |
| 8. Crumrine, Kessel <sup>11</sup> . . . . .              | California . . . . .  | 1931     |
| 9. Müller <sup>12</sup> . . . . .                        | Java . . . . .        | 1932     |
| 10. Hansmann, Schenken <sup>13</sup> . . . . .           | Iowa . . . . .        | 1933     |
| 11. Dodd, Tompkins <sup>14</sup> . . . . .               | Tennessee . . . . .   | 1934     |
| 12. Negroni <sup>15</sup> . . . . .                      | Argentina . . . . .   | 1938     |
| 13. Agress, Gray <sup>17</sup> . . . . .                 | Missouri . . . . .    | 1939     |
| 14. Amolsch, Wax <sup>18</sup> . . . . .                 | Michigan . . . . .    | 1939     |
| 15. Shaffer, Shaul, Mitchell <sup>19</sup> . . . . .     | Virginia . . . . .    | 1939     |
| 16. deAlmeida, daSilva Lacaz <sup>20</sup> . . . . .     | Brazil . . . . .      | 1939     |
| 17. Clemens, Barnes <sup>21</sup> . . . . .              | Kentucky . . . . .    | 1940     |
| 18. Negroni <sup>16</sup> . . . . .                      | Argentina . . . . .   | 1940     |
| 19. Reid, Scherer, Irving <sup>22</sup> . . . . .        | Virginia . . . . .    | 1940     |
| 20. Gunter, Lafferty <sup>23</sup> . . . . .             | Alabama . . . . .     | 1940     |
| 21. Williams, Cromartie <sup>24</sup> . . . . .          | Tennessee . . . . .   | 1940     |
| 22. Humphrey <sup>4</sup> . . . . .                      | Michigan . . . . .    | 1940     |
| 23. Humphrey <sup>4</sup> . . . . .                      | Michigan . . . . .    | 1940     |
| 24. Meleney <sup>6</sup> . . . . .                       | Tennessee . . . . .   | 1940     |
| 25. Meleney <sup>6</sup> . . . . .                       | Tennessee . . . . .   | 1940     |
| 26. Brown, Havens, Magath <sup>13</sup> . . . . .        | Texas . . . . .       | 1940     |
| 27. Parsons, (Meleney) <sup>6, 46, 69</sup> . . . . .    | Michigan . . . . .    | 1940     |
| 28. Weller (Meleney) <sup>6</sup> . . . . .              | Ohio . . . . .        | 1940     |
| 29. Parsons (Meleney) <sup>6, 46, 69</sup> . . . . .     | Michigan . . . . .    | 1940     |
| 30. Forry Culbertson (Meleney) <sup>6</sup> . . . . .    | Indiana . . . . .     | 1940     |
| 31. Martin, Silber (Meleney) <sup>6, 62</sup> . . . . .  | California . . . . .  | 1940     |
| 32. Currie (Meleney) <sup>6</sup> . . . . .              | Indiana . . . . .     | 1940     |
| 33. Villela, Para (Meleney) <sup>6, 49</sup> . . . . .   | Brazil . . . . .      | 1940     |
| 34. Blache, Moore (Meleney) <sup>6</sup> . . . . .       | Missouri . . . . .    | 1940     |
| 35. Mantell, Troy (Meleney) <sup>6</sup> . . . . .       | Florida . . . . .     | 1940     |
| 36. Rhodes, Conant, Glesne <sup>44</sup> . . . . .       | Indiana . . . . .     | 1941     |
| 37. Anderson, Michelson, Dunn <sup>45</sup> . . . . .    | Tennessee . . . . .   | 1941     |
| 38. deAlmeida, daSilva Lacaz <sup>20</sup> . . . . .     | Brazil . . . . .      | 1941     |
| 39. VanPernis, Benson, Hollinger <sup>41</sup> . . . . . | Illinois . . . . .    | 1941     |
| 40. Wright, Hachtel <sup>47</sup> . . . . .              | Maryland . . . . .    | 1941     |
| 41. Scott <sup>48</sup> . . . . .                        | Kentucky . . . . .    | 1941     |

TABLE I—*Continued*

| Authors and References *                                         | Locale                | Reported |
|------------------------------------------------------------------|-----------------------|----------|
| 42. Hild <sup>50</sup> .....                                     | Tennessee.....        | 1942     |
| 43. Derry, Card, Wilson, Duncan <sup>27</sup> .....              | England.....          | 1942     |
| 44. Ramsey, Applebaum <sup>51</sup> .....                        | Michigan.....         | 1942     |
| 45. Henderson, Pinkerton, Moore <sup>42</sup> .....              | Michigan.....         | 1942     |
| 46. Key, Large <sup>52</sup> .....                               | Missouri.....         | 1942     |
| 47. Palmer, Amolsch, Shaffer <sup>39</sup> .....                 | Michigan.....         | 1942     |
| 48. Simson, Parnetson <sup>54</sup> .....                        | South Africa.....     | 1942     |
| 49. Dean <sup>55</sup> .....                                     | Missouri.....         | 1942     |
| 50. German, Ashmun, Dille <sup>56</sup> .....                    | Ohio.....             | 1943     |
| 51. Perrin, Baez <sup>57</sup> .....                             | Mexico.....           | 1943     |
| 52. Broders, Dochat, Herrell, Vaughan <sup>58</sup> .....        | Oklahoma.....         | 1943     |
| 53. Boltjes <sup>25</sup> .....                                  | Kansas.....           | 1943     |
| 54. Wood, Moore <sup>59</sup> .....                              | Missouri.....         | 1943     |
| 55. Balina, Herrera, Bosq, Negroni <sup>16</sup> .....           | Argentina.....        | 1943     |
| 56. Buie <sup>60</sup> .....                                     | North Carolina.....   | 1943     |
| 57. Thomas, Morehead <sup>61</sup> .....                         | North Carolina.....   | 1943     |
| 58. Moore, Jorstad <sup>26</sup> .....                           | Missouri.....         | 1943     |
| 59. Sherwin, Allen (Moore and Jorstad) <sup>26</sup> .....       | Missouri.....         | 1943     |
| 60. Burden, Chapman (Moore and Jorstad) <sup>26</sup> .....      | New York.....         | 1943     |
| 61. Dominguez, Golden (Moore and Jorstad) <sup>26</sup> .....    | Ohio.....             | 1943     |
| 62. Schlumberger, Service <sup>63</sup> .....                    | Pennsylvania.....     | 1944     |
| 63. Beamer, Smith, Barnett <sup>35</sup> .....                   | Missouri.....         | 1944     |
| 64. Colvin, Gore, Peters <sup>64</sup> .....                     | Georgia.....          | 1944     |
| 65. Kemper, Bloom <sup>65</sup> .....                            | Michigan.....         | 1944     |
| 66. Stingily (Parsons and Zarafonetis) <sup>69</sup> .....       | Mississippi.....      | 1945     |
| 67. Gray (Parsons and Zarafonetis) <sup>69</sup> .....           | Missouri.....         | 1945     |
| 68. Parsons, Zarafonetis <sup>69</sup> .....                     | Michigan.....         | 1945     |
| 69. Steiner (Parsons and Zarafonetis) <sup>69</sup> .....        | Illinois.....         | 1945     |
| 70. Brown, Poncher (Parsons and Zarafonetis) <sup>69</sup> ..... | Illinois.....         | 1945     |
| 71. Parsons, Zarafonetis <sup>69</sup> .....                     | Michigan.....         | 1945     |
| 72. Dawson (Parsons and Zarafonetis) <sup>69</sup> .....         | Tennessee.....        | 1945     |
| 73. Manchester (Parsons and Zarafonetis) <sup>69</sup> .....     | Washington, D. C..... | 1945     |
| 74. Hunter (Parsons and Zarafonetis) <sup>69</sup> .....         | Washington, D. C..... | 1945     |
| 75. Burns (Parsons and Zarafonetis) <sup>69</sup> .....          | Louisiana.....        | 1945     |
| 76. Dawson (Parsons and Zarafonetis) <sup>69</sup> .....         | Tennessee.....        | 1945     |
| 77. R. A. Moore (Parsons and Zarafonetis) <sup>69</sup> .....    | Missouri.....         | 1945     |
| 78. Parsons, Zarafonetis <sup>69</sup> .....                     | Michigan.....         | 1945     |
| 79. Ziegler.....                                                 | Pennsylvania.....     | 1945     |

\* Authors in parentheses are those who first cited the cases.

TABLE II  
Geographic Distribution

|                           |    |                   |    |
|---------------------------|----|-------------------|----|
| Alabama.....              | 1  | Ohio.....         | 3  |
| California.....           | 2  | Oklahoma.....     | 1  |
| District of Columbia..... | 2  | Pennsylvania..... | 2  |
| Florida.....              | 1  | Tennessee.....    | 8  |
| Georgia.....              | 1  | Texas.....        | 1  |
| Illinois.....             | 3  | Virginia.....     | 2  |
| Indiana.....              | 3  | Canal Zone.....   | 3  |
| Iowa.....                 | 1  | Philippines.....  | 1  |
| Kansas.....               | 1  | Argentina.....    | 3  |
| Kentucky.....             | 2  | Austria.....      | 1  |
| Louisiana.....            | 1  | Brazil.....       | 3  |
| Maryland.....             | 1  | England.....      | 1  |
| Michigan.....             | 12 | Honduras.....     | 1  |
| Minnesota.....            | 1  | Java.....         | 1  |
| Mississippi.....          | 1  | Mexico.....       | 1  |
| Missouri.....             | 10 | South Africa..... | 1  |
| New York.....             | 1  |                   |    |
| North Carolina.....       | 2  | Total.....        | 79 |

The characteristics of the fungus have also been studied by Ciferri,<sup>30</sup> Redaelli,<sup>31</sup> Howell,<sup>32</sup> daRocha-Lima,<sup>5</sup> Negroni<sup>15</sup> and others. Redaelli, Ciferri and Howell believe that there is only one species of histoplasma. A discussion of the difficult problem of classification of the fungus is given by Moore and Jorstad.<sup>26</sup>

*Histoplasma capsulatum* in tissues is usually a round or oval yeast-like cell which sometimes shows budding. It ranges from one to five micra or more in the long diameter, but is usually about three micra. It has a hyaline capsule, sometimes a large vacuole and a large central or eccentric nuclear granule. The granule is round or crescentic, stains deeply and is usually surrounded by a clear zone. There is no accessory chromatin dot or kinetoplast as seen in Leishman-Donovan organisms of kala-azar.

The organism can be demonstrated but does not stain well with ordinary stains. My hematoxylin-eosin tissue stain technic<sup>33</sup> demonstrates it very well. That of Tomlinson and Grocott<sup>34</sup> which was developed for malarial protozoa in tissues is also very good. We leave out the ammonium sulfide solution for removing malarial pigment.

*Histoplasma capsulatum* grows readily on a large variety of ordinary media including Sabouraud's media, potato-dextrose media, blood agar, etc. It grows well at 37° C. and slower at room temperature (three to 10 days).

The fungus is aerobic but may grow in partial anaerobiasis. The filamentous cultured forms may be transformed to the budding yeast-like forms by growing them on sealed blood agar slants at 37° C. According to Beamer et al.<sup>35</sup> the fungus is resistant to drying and to temperatures between 5° and 8° C. They found that it could be killed in milk by heating for 20 minutes between 62° and 63° C.

The colony has an irregular surface, is brown and glabrous. With aging and on dry portions of media it is white and cottony. In cultures, the fungus forms septate, branching hyphae and according to Conant<sup>29</sup> "thick-walled chlamydospores with a tuberculate sculpturing of the outer wall." Filtered ultraviolet rays show no fluorescence. Moore and Jorstad<sup>26</sup> give a good short description of the cultured forms.

Laboratory animals including mice, rats, guinea-pigs, cats, dogs and monkeys can be infected by injection of the cultures as demonstrated first by DeMonbreun,<sup>3</sup> Hansmann and Schenken<sup>13</sup> and others.

In 1939 DeMonbreun<sup>3</sup> found the disease occurring naturally in a dog and in 1944 Thuringer<sup>36</sup> reported another similar case. The dog and other animals are therefore suspected of being carriers which might transmit the disease directly or indirectly to man. The disease was discovered in a ferret by Levine, Dunlap and Graham<sup>37</sup> and in mice by Sangiorgi.<sup>38</sup> *Histoplasma capsulatum* has not been found free in nature outside of animal hosts. Although animal vectors are suspected, the mode of transmission of the disease is unknown. It is said that animals are carriers of other fungi, principally the dermatophytes which produce ringworm in man.

The portal of entry has not been definitely determined. The pulmonary cases suggest inhalation. The skin lesions suggest local inoculation. The mouth and intestinal lesions suggest ingestion. The portal of entry may therefore be any of these. The possibility of insect vectors or fomites must also be considered in view of our lack of knowledge on this subject.

The symptoms presented by the various cases reported have been protean. The characteristic symptoms are: irregular pyrexia, loss of weight, anemia, leukopenia, splenomegaly, hepatomegaly and lymphadenopathy. Some cases present pulmonary or upper respiratory signs and symptoms. Moore and Jorstad<sup>26</sup> have recently listed 22 cases showing ear, nose or throat involvement. Some cases have skin lesions, others show mucous membrane lesions including signs and symptoms of intestinal ulceration. Some cases have shown evidence of adrenal involvement. The disease may be acute, subacute or chronic; localized or general; but according to reports it is invariably fatal.

All races and both sexes have been affected. A considerable number of cases have appeared in infants. Reported cases have ranged from seven weeks of age to over 70. From the onset of the first known symptoms, the disease has run from five weeks to as long as 15 years.

Pathologically, the disease is an infectious granuloma with "invasion" of the reticuloendothelial system by the fungous forms. Lesions occur in the skin, mucous membranes, lymph nodes, liver, spleen, lungs, bone marrow and adrenal glands. They have also been reported in the kidneys, prostate, heart, endocardium, pleura, bone, brain, ear, nose, larynx, large and small intestine, periosteum, joints and other sites. Including the case reported in this paper there have been at least 21 cases showing adrenal gland involvement.

Grossly, the lesions vary from small, barely visible nodules to large granulomatous masses which show necrosis and they may show interstitial hemorrhage. Surface lesions may ulcerate. Necrotic areas have white, dirty gray or grayish-yellow color and may show red to reddish-black areas due to hemorrhage.

Histoplasmosis is primarily an infectious granulomatous disease which can involve many of the tissues of the body. The reticuloendothelial phagocytosis of the fungus is regarded as a defense mechanism. The disease is not exclusively one of the reticuloendothelial system as so often stated. Palmer, Amolsch and Shaffer<sup>29</sup> formerly called attention to this point.

Microscopically, the lesions are characterized by the presence of large numbers of large reticuloendothelial cells which contain a few to enormous numbers of the characteristic yeast-like fungus parasites. There are variable numbers of plasma cells, lymphocytes, polymorphonuclear cells, eosinophiles and fibrocytes. There are no circumscribed tubercles but there may be a few giant cells of the Langhans or foreign-body type and there is a variable amount of necrosis. Necrosis is usually focal but in some lesions it has been extensive.

The fungi may be found in the monocytes of blood, the reticuloendothelial cells, in endothelium, in alveolar epithelium and occasionally in mucous membrane or glandular epithelium. They are also found to some extent in intercellular spaces. The organisms are readily found in reticuloendothelial cells surrounding areas of necrosis.

The diagnosis can be made during life but the great majority of cases have been diagnosed from autopsy specimens. The fungous forms may be identified during life by blood culture and subsequent animal inoculation. They have been found in the large mononuclear cells of blood films, prepared with Wright's or Giemsa stain, but supravital blood smears prepared with neutral red are better. They can be found in smears or sections of liver, spleen, lymph node, bone marrow, cutaneous or mucous membrane lesions.

Specific cutaneous tests for the disease have been developed by Zarafonetis and Lindberg<sup>40</sup> and by VanPernis, Benson and Hollinger.<sup>41</sup> This may prove to be a diagnostic aid in cases where lesions are inaccessible.

Henderson et al.<sup>42</sup> have suggested examination of the stool for *Histoplasma capsulatum* in cases with suspected intestinal lesions.

Biopsy and autopsy tissues will reveal the fungi when present, if stained by any one of various methods including iron-hematoxylin, Gram, Geimsa, Wright, Goodpasture, hematoxylin-eosin or the technic of Tomlinson and Grocott.

The disease must be differentiated from kala-azar, tuberculosis, lymphoma, leukopenic leukemia, noma, rhinoscleroma, carcinoma, otitis media and others, including Addison's disease due to tumor or tuberculosis of the adrenal glands. The diagnosis of the disease during life and at autopsy depends primarily (as with other relatively uncommon diseases) upon the alertness of the clinician and the laboratory worker. Diagnosis of the disease has been made during life in at least 30 cases.

Treatment has been of no avail. Cases diagnosed during life have been treated with potassium iodide, sodium iodide, roentgen-ray, neoarsphenamine, radon seeds, sulfarsenal, emetine, sulfonamide drugs, vitamins, quinine, potassium arsenite, Fowler's solution, atabrine, bismuth, liver extract, pentnucleotide, surgical excision, fuadin, antimony tartrate, neostam, and ionized copper. Cases have been reported ante mortem but the great majority of these have died subsequently. A few have had no follow-up reports to show that they survived.

One unfavorable report was found on the use of penicillin. Gentian violet is effective in treating thrush and might be tried for histoplasmosis. There are other dyes that might be tried also. As the disease is fatal, heroic therapy would seem justifiable. Mercury is often effective when applied topically to fungous skin infections. It is therefore suggested that mercury, mercurochrome and other organic mercurials might be worthy of trial in this disease. Thymol is often an effective fungicide. Histoplasmosis may be a local disease initially but sooner or later it becomes systemic. This would indicate the probable ineffectiveness of any topical application. Search must be made for an effective fungicide which may be given parenterally.

#### CASE REPORT

R. S., a 58 year old, white woman, born in Hungary, came to this country at the age of 20 and lived in this city for 38 years. She was a housewife and domestic and had a husband and three children living and well. She was admitted to the surgical service on October 10, 1925 and had an uneventful hysterectomy for a large submucous fibroid.

Patient was well until 1942 (two years before last hospitalization) when she was found to have diabetes. The disease remained non-symptomatic and she took 20 units of protamine-zinc insulin each day.

Two months before hospitalization, patient had "influenza" and remained in bed because of slightly productive cough, chills, fever and prostration. She was orthopneic at times and had some swelling of the abdomen but none of extremities.

During this time, patient became progressively weaker. Pain developed in the right upper abdominal quadrant, in the right lumbar region and it radiated down both legs. The legs became extremely painful and weak and patient was unable to stand or walk and had to be carried. At no time were the legs swollen. Shortly before admission, patient had a severe epistaxis. Her appetite was poor and she lost 70

pounds in weight, from 215 to 145 pounds. There was no vomiting, diarrhea or tarry stools. Patient was constipated and took laxatives. There were no genito-urinary signs or symptoms. Blood pressure was about 205 mm. Hg systolic.

Patient was admitted to St. Luke's Hospital, February 16, 1944, on the medical service with the above symptoms. Her chief complaint was marked general weakness with pain in the right side, back and legs.

Temperature was 102° F., pulse 120, respirations 24, blood pressure 140 mm. Hg systolic and 60 mm. diastolic. She was sweating profusely and was obviously very weak and ill but was mentally alert and coöperative. There were râles in the bases of both lungs. The heart was regular but a moderately loud systolic murmur was heard at the apex.

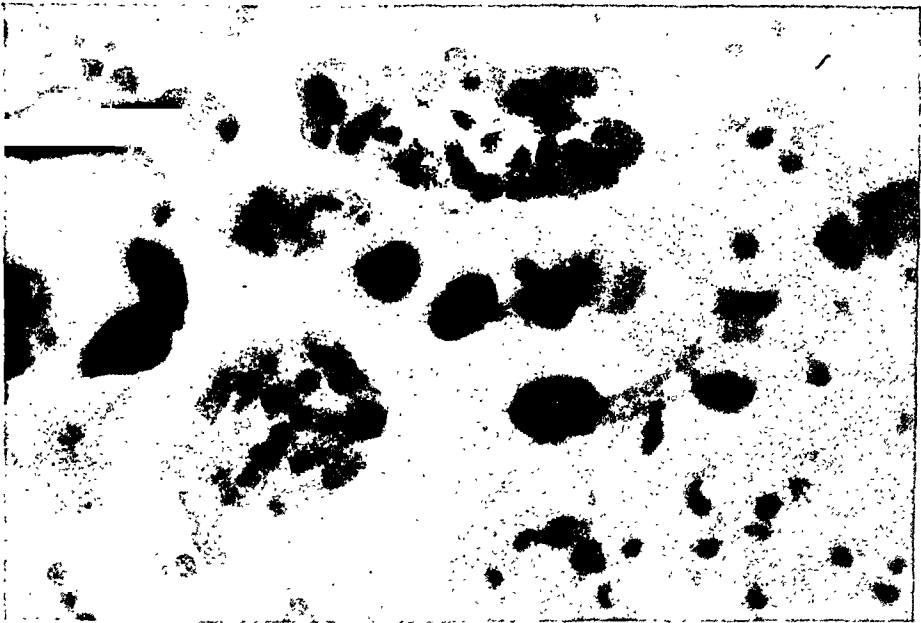


FIG. 1. Photomicrograph (2250  $\times$ ), *Histoplasma capsulatum* in section of the adrenal.

The abdomen was distended and the liver edge was palpated on a level with the umbilicus. The liver "filled the right flank."

After she came to the hospital the pain, described above, disappeared but her condition gradually became worse. She took practically no nourishment. She developed incontinence of urine and feces, had periods of vomiting and sweating, and periods of semicomatose.

There was a spiking temperature curve each one or two days. It ranged between 96° and 103° F. The pulse rate varied between 72 and 124 and the respirations between 16 and 36.

On February 28, twelve days following admission, the patient died. No definite diagnosis had been made other than mild diabetes, but it was thought likely that she might have carcinoma of the liver.

Treatment had been supportive only and included digitalis, codein and nembutal. No insulin was given while the patient was in the hospital and there was no glycosuria as shown by frequent tests.

On February 16, a roentgenogram of the chest showed considerable thickening of the bronchial markings. There was no evidence of consolidation. The heart shadow was increased in size.

On February 17, the blood urea nitrogen was 26 mg.; the blood sugar 131 mg.; erythrocytes 4.7 million; leukocytes 5.5 thousand; hemoglobin 13 grams; juvenile

leukocytes 26; segmented leukocytes 34; lymphocytes 40. The urine showed a specific gravity of 1.014, a pH of 4, albumin one plus, and numerous erythrocytes. The icterus index was 8.

Roentgenographic studies of the gastrointestinal tract on February 18 and 20 showed no evidence of organic lesions.

February 19, the Kolmer-Wassermann and the Boerner precipitation tests were negative.

On February 21, the urinalysis showed a specific gravity of 1.009, a pH of 4, a heavy trace of albumin, occasional leukocytes and 8 to 10 erythrocytes per high power field.

On February 23, the blood urea nitrogen was 26 mg. and the sedimentation rate 93 mm. in one hour, using the Westergren method. The prothrombin was 78 per cent of normal.

#### ABSTRACT OF AUTOPSY PROTOCOL

*The lungs.* The lower half of both lower lobes showed moderate early red hepaticization. The remainder of the lung tissue showed congestion and edema.

*The heart* weighed 390 grams. The left ventricle was hypertrophied to 21 mm. in thickness. The valves showed no gross changes. The coronary arteries and aorta were moderately atherosclerotic. There were small focal hemorrhages in the endocardium of the left ventricle.

*The liver* was considerably enlarged, especially the left lobe. The lower border of the liver was on a level with the umbilicus. The capsule was not thickened but the surface was finely granular. The liver cut readily and there was no eversion of the cut edges. It was somewhat lighter in color than usual but appeared moderately congested.

*The lymph nodes* above the head of the pancreas were enlarged. Their average size was about that of a hazelnut. Five or six of these nodes were loosely connected to each other by areolar tissue.

*The spleen* was about twice normal size and was soft in consistency. It had a light brown color. Follicles were not readily seen.

*The adrenal glands* were greatly enlarged, nodular and very irregular in shape. The left measured 9 by 5 by 3 cm. and the right 7 by 4 by 2 cm. Cut sections showed grayish-yellow, soft tissue. There were dark red areas due to hemorrhage. There were also grayish-red and cream colored, soft areas of necrosis. At several places one could see remnants of thin, yellow cortical tissue. No medullary tissue was seen. There were no tubercles.

The internal genitalia had been removed surgically and the remainder of the organs showed no significant gross changes.

#### HISTOPATHOLOGY

*The adrenal glands* showed severe and extensive necrosis and massive replacement by granulomatous tissue. Remnants of cortex were present but no medullary tissue was found. The granulomatous masses consisted of a small amount of fibrous tissue containing plasma cells, lymphocytes and a few polymorphonuclears. There were a few scattered giant cells. There were large and small masses of very large cells of the reticuloendothelial type. Outside of the necrotic areas, these cells were seen to contain large numbers of the characteristic yeast-like forms of the fungus *Histoplasma capsulatum*. The lesions simulated tuberculosis in many respects; however, there were no formations of typical circumscribed tubercles. Fungous forms could be seen occasionally between or in residual cortical cells.

*In the liver* there were numerous scattered, small, granulomatous infiltrations, but no necroses. These granulomata were similar to those described below in other tissues.

In the lungs there were scattered, small, microscopic, interstitial or intra-alveolar, granulomatous formations consisting mostly of reticuloendothelial cells with a few giant cells and some plasma cells.

The abdominal lymph nodes showed marked edema and great dilatation of the sinusoids. The latter contained numerous reticuloendothelial cells, plasma cells, occasional lymphocytes and some eosinophiles. There were occasional microscopic granulomata consisting of compact groups of reticuloendothelial cells.

The spleen did not show as much edema as the lymph nodes but there were occasional scattered microscopic granulomata similar to those in the lungs, liver and lymph nodes. The splenic corpuscles had nearly all disappeared.

The granulomata, of microscopic size, found in the lungs, liver, lymph nodes and spleen are believed to be due to histoplasmosis but organisms could not be satisfactorily demonstrated in them. These granulomata consist primarily of groups of reticuloendothelial cells about which are plasma cells and variable numbers of other cells including occasional Langhans' cells. In the enlarged lymph nodes and spleen, one sees an occasional giant cell of the Sternberg-Reed type. The reticuloendothelial cells in some of the lesions show phagocytosis of a small amount of cellular debris.

The heart showed moderate cloudy swelling, some edema and slight atrophy of muscle fibers. There were occasional small scarred areas due to arteriosclerotic anemia. The coronary arteries showed moderate fibrosis and atherosclerosis.

The kidneys showed moderate arteriolonephrosclerosis.

Changes in other organs were not remarkable. The autopsy diagnoses were: (1) Histoplasmosis, both adrenal glands, severe; generalized, mild. (2) Hypertensive cardiovascular-renal disease, moderate. (3) Diabetes mellitus, mild (from history).

#### COMMENT

This case of histoplasmosis had the characteristic findings of irregular fever, weight loss, respiratory symptoms, leukopenia, splenomegaly and hepatomegaly. In addition, there was extreme muscular weakness and finally death, due no doubt to adrenal insufficiency.

The principal lesions were in the adrenal glands. These organs were replaced by large, quite necrotic granulomatous masses in the sections of which were demonstrated enormous numbers of yeast-like fungous forms of *Histoplasma capsulatum* as shown in the photomicrograph.

The lesions of histoplasmosis differ from tuberculosis in several respects: There are no circumscribed tubercles. The focal granulomata are not walled off by a mantle of lymphocytes. Lymphocytes are present but in very small numbers as compared to the typical tuberculous lesions. Plasma cells are generally quite abundant and there are more polymorphonuclears and eosinophiles than generally seen in tuberculosis. The disease must be differentiated from other granulomata by demonstrating the fungi.

#### SUMMARY

1. Another case of histoplasmosis is recorded. The principal lesions were in the adrenal glands but the patient presented nearly all the common signs and symptoms of the disease. The diagnosis was not made until after death.

2. Histoplasmosis seems to be spreading and there are at this time 79 recorded cases.

3. The medical profession should be on the alert for further cases as it is entirely probable that many cases of this highly lethal disease go unrecognized.



4. Suggestions concerning the treatment for the disease and for the histologic demonstration of the fungus have been made.

5. The lesions produced by *Histoplasma capsulatum* are essentially granulomatous and they may involve many different structures of the body. They are not necessarily confined to the reticuloendothelial system. Reticuloendothelial proliferation with phagocytosis of the fungous forms is probably the chief defense of the body against the disease.

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## MULTIPLE MYELOMA SIMULATING HYPER-PARATHYROIDISM \*

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HYPERCALCEMIA, hypophosphatemia, and increased excretion of calcium and phosphorus in the urine characterize the metabolic changes in clinical hyperparathyroidism. The appearance of a high blood calcium in such conditions as multiple myeloma and metastatic carcinoma of bone has led to speculation as to whether this is simply incident to diseases causing rapid bone destruction or whether true hyperactivity of the parathyroid glands exists. Bulger and Barr<sup>1</sup> were inclined toward the latter theory, as it is known (a) that it is difficult to raise the serum calcium even by giving large quantities of calcium by mouth, and (b) that the parathyroids readily undergo hyperplasia. They reported the autopsy of a case of multiple myeloma in which the three parathyroid glands found were all moderately enlarged and hyperplastic. Enzer and Lieberman<sup>2</sup> reported a case of multiple myeloma in which parathyroidectomy was performed and parathyroid tissue (confirmed by frozen section) presumed to have been removed. Death occurred from bronchopneumonia on the third post-operative day. No further gland tissue was discovered at autopsy despite extensive dissection. However, on section of blocks of tissue a microscopic parathyroid gland was found. Hyperplasia was not present; on the contrary, it was thought that atrophy had occurred, possibly as an aftermath of prolonged stimulation and previous hypertrophy. Finally, the occurrence of the third possibility, that the

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parathyroid glands are entirely normal in multiple myeloma with hypercalcemia, was reported by Caylor and Nickel.<sup>3</sup> Likewise, Mason and Warren<sup>4</sup> in a case of metastatic carcinoma simulating hyperparathyroidism found only adenocarcinomatous change in the parathyroids and no histological evidence of hyperplasia. On the whole, however, descriptions of the parathyroid glands are almost uniformly omitted in the published necropsy reports of multiple myeloma.<sup>5, 6, 7</sup> As to the possibility that the glands found might happen to be ones which did not show hyperplasia, Castleman and Mallory<sup>8</sup> established in a large series of autopsies on true hyperparathyroidism that if hyperplasia were present, all the parathyroid tissue in the body underwent those changes.

The following case is of interest both because of the problems in differential diagnosis which it presented, and the fact that the parathyroid glands were found to be grossly and histologically normal.

#### CASE REPORT

Mrs. R. B., a 38 year old housewife of English descent, was admitted to the hospital on December 10, 1944 with the immediate complaint of "stomach and bowel trouble," and of pain in the right shoulder. The family history was non-contributory. A review of her past history revealed little in the way of previous illnesses. At the age of 25 she had had an appendectomy, and in 1942 three attacks of kidney stone colic. She had been married 23 years and had had one normal pregnancy and one miscarriage. Menstruation began at the age of 13 and had always been regular and normal.

*Present Illness:* She had seemed quite well until seven months before admission when she rather suddenly began to have nausea and bouts of generalized abdominal pain. She saw various physicians who noted a progressive anemia. In October she was given a blood transfusion at another hospital and seemed somewhat improved for a time. However, she continued to lose weight and strength and soon began to have a severe, remitting type of pain in the back and right upper extremity involving particularly the shoulder and hand. At times even the weight of the bedclothes was intolerable. The joints themselves were never swollen, and motion was limited only by pain. For five weeks prior to admission there had been much upper abdominal cramping pain, aggravated by food of all types and often associated with distention and vomiting. Obstipation was extreme, and laxatives and enemata had been used without effect. Her last menstrual period had occurred in April 1944.

*Physical Examination:* Temperature was 98.0, pulse 85, respirations 16, and blood pressure 88 mm. Hg systolic and 50 mm. diastolic. When first examined, the patient was in acute pain and distress. At frequent intervals she vomited small amounts of bile-stained fluid. She was unable to turn in bed and seemed to have exquisite tenderness over the right shoulder and entire spine. Periarticular structures were well preserved and joint motion good, except in the right upper extremity where it was limited by pain. One bead-like enlargement was palpable over the eighth rib in the right anterior axillary line. There was marked wasting of the muscles, atrophy and dryness of the skin, and pallor of the skin and mucous membranes. A small decubital ulcer was present over the right sacrum. Eyes, nose and throat were not remarkable. The tongue was red and dry. A few small non-tender axillary nodes were present. The neck was thin and no thyroid enlargement or masses were noted. The chest was clear, the heart normal except that the pulmonic second sound was greater than the aortic second. The abdomen was distended with gas, and there was marked tenderness in the epigastrium. No peristaltic waves were seen. The liver and spleen were not palpable, and there were no other masses. Rectal examination revealed a normal cervix; fecal masses were not present.

*Laboratory:* Urine: specific gravity was 1.004, the reaction neutral, albumin 0, sugar 0, red blood cells 0, pus 3 (clumps). Blood: there was 56 per cent (9.5 gm.) of hemoglobin; the red blood cell count was 3,120,000; white blood cell count 4,900 with 48 per cent lymphocytes, 50 per cent neutrophils and 2 per cent monocytes. No reticulated cells were seen. Platelet count was 176,000. Wassermann and Kahn



FIG. 1. Roentgenogram showing trabeculation in head of humerus.

reactions were negative. The Rh factor was positive. A 24-hour urine specimen was negative for Bence-Jones protein. Sedimentation rate was 16 corrected (Win-trobe method). Blood chemistry: total serum protein 4.62 gm., with albumin 3.81, globulin 0.81 (AG ratio 4.7), non-protein nitrogen, 40 mg. per cent, serum calcium \* 16 mg. per cent, serum phosphorus † 2.9 mg. per cent and alkaline phosphatase 1.93 Bodansky units per 100 c.c. A 24 hour urine calcium excretion on a low calcium

\* Method of Kramer-Tisdall, Clark-Collip modification.

† Method of Youngburg.

intake was 151.37 mg. Roentgen-rays of almost the entire skeleton were taken and showed various extensive areas of destruction involving the pelvis, lumbar spine, humerus, femurs, ribs, clavicles and skull. The hands, wrists and feet were negative. A flat plate of the abdomen showed no renal calculi. Many of the lesions were punched out in type, but other areas were diffusely decalcified and showed good trabeculation (figure 1). Various selected rib lesions were exactly like those of metastatic carcinoma, but others in the long bones resembled those of multiple myeloma. The consensus of radiological opinion, however, was in favor of osteitis fibrosa cystica, a type lesion of which is shown in figure 2.



FIG. 2. Roentgenogram of pelvis showing multiple cysts.

*Hospital Course:* The first phase of the hospital course was concerned with combating the episodes of paralytic ileus which occurred three different times. Intravenous glucose, saline and vitamins were used, and these, with the passing of Levine and Miller-Abbott tubes, were each time successful in the relief of the obstruction, which by roentgen-ray seemed to be proximal to the splenic flexure of the colon. Three blood transfusions raised the hemoglobin to 88 per cent and the red cell count to 4,240,000. Ten days after admission the serum calcium was 14 mg. per cent, the phosphorus 3.2 mg. per cent and the alkaline phosphatase 2.92 Bodansky units per 100 c.c. The pain in the shoulder was quite variable in intensity, and on some days she could move about as freely as her weakness permitted. She ran an essentially afebrile course.

A diagnosis of hyperparathyroidism having been made (see discussion below), the patient was submitted to exploration of the neck. Two inferior parathyroid glands were located and a sub-total resection of the right plus a total resection of the left performed. The superior parathyroids were not demonstrated. Following operation, which the patient withstood very well, there was symptomatic improvement in

that abdominal distention and pain were diminished, but the serum calcium remained at a high level, being 15.5 mg. per cent on the fourth post-operative day. Needless to say, no signs of tetany developed. Histological examination of the parathyroids showed normal gland structure (figure 3), there being none of the changes of either adenoma or hyperplasia. It became apparent that before further exploration for an adenoma was carried out the question of multiple myeloma would have to be recon-

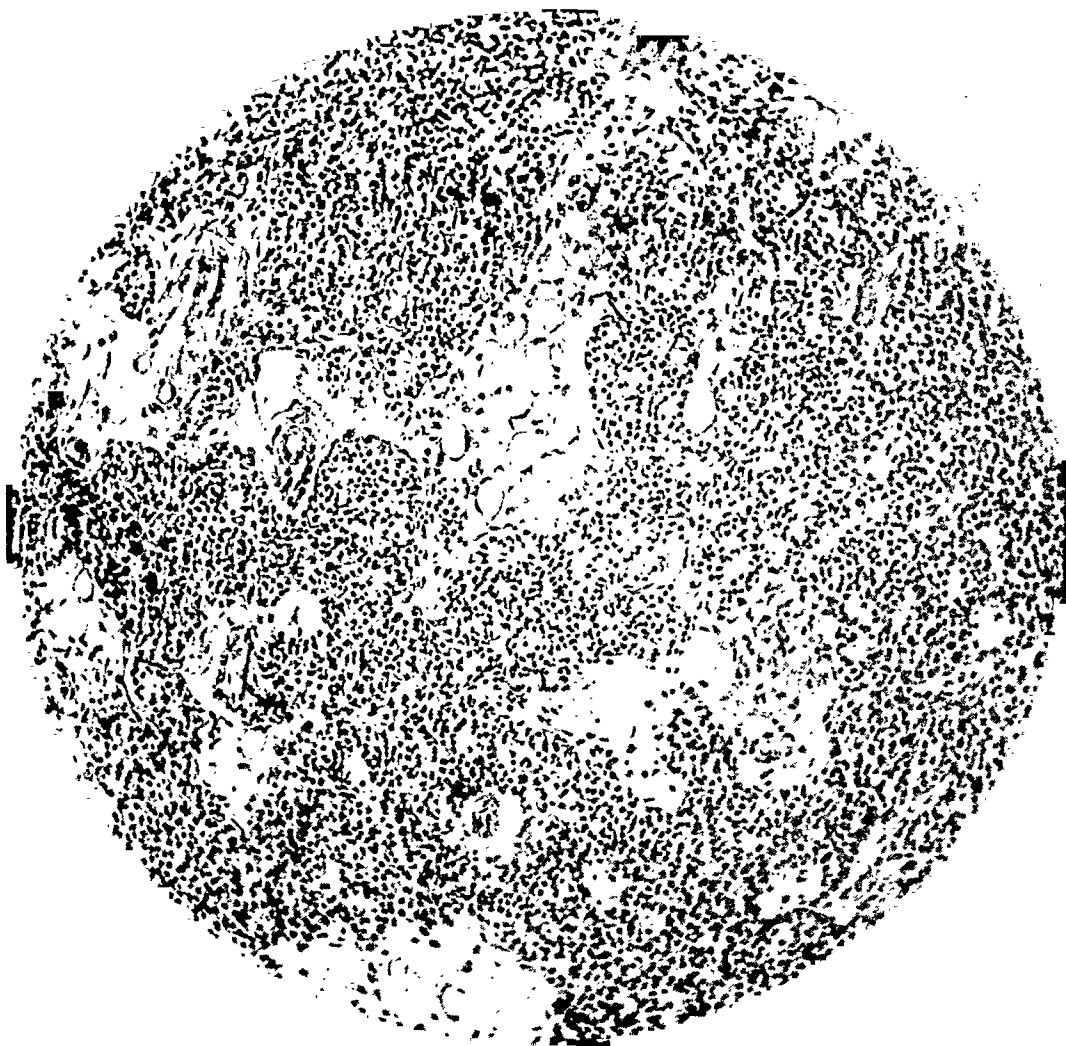


FIG. 3. Section of parathyroid gland, histologically normal.  $\times 129$ .

sidered. Two sternal aspirations were unsuccessful, so bone marrow biopsy was belatedly performed. A red, gelatinous material was obtained which showed 72 per cent typical myeloma cells (figure 4).

The patient was discharged on her eleventh post-operative day, improved to the extent that her gastrointestinal complaints were minimal. Her blood calcium was 14.3 mg. per cent, blood phosphorus 2.22 mg. per cent and blood phosphatase 3.10 Bodansky units per 100 c.c. Three weeks later on a return trip to the Clinic, these values were 13.9, 2.38 and 5.71, respectively. A course of roentgen-ray therapy, suggested for possible palliation, was refused. She grew steadily worse and died on



March 22, 1945. Autopsy showed extensive replacement of marrow with myeloma cells. No further parathyroid tissue was found.

#### DIFFERENTIAL DIAGNOSIS

The clinical and laboratory findings common to both multiple myeloma and hyperparathyroidism which were present in this case were as follows: Progressive weakness and anemia, bone pain, abdominal pain, vomiting, bone cysts and

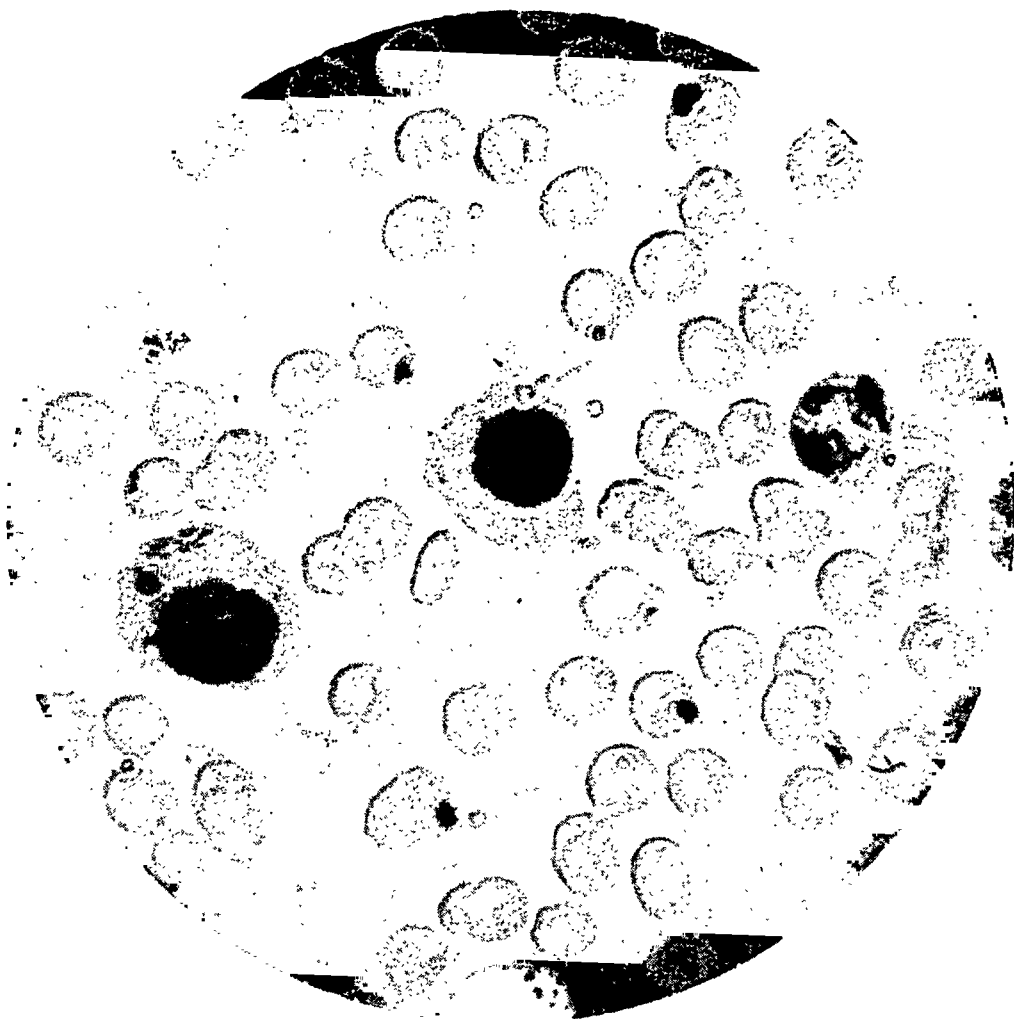


FIG. 4. Myeloma cells in a smear taken at sternal biopsy.

pathological fractures by roentgen-ray, and high blood calcium. Findings frequently present in multiple myeloma, but absent here, were Bence-Jones proteinuria, elevated total serum proteins, reversed albumin-globulin ratio, and evidence of kidney insufficiency. Findings frequently present in hyperparathyroidism, but absent or doubtful here, were a low blood phosphorus, a negative calcium balance (high urinary calcium excretion), and an increased blood phosphatase. In this case, one blood phosphorus determination was definitely low (2.22), the others low normal. Only post-operatively did the phosphatase level

rise above normal. The history of kidney stones in the past was quite suggestive of hyperparathyroidism.

The question can well be raised as to why bone marrow biopsy was not performed prior to parathyroidectomy. It was in fact so scheduled, but final radiological opinion was so firmly in favor of hyperparathyroidism that exploration of the neck was carried out first, and at such length, as it turned out, that bone marrow biopsy was not considered feasible as a supplementary procedure at the same time. If pitfalls in diagnosis are to be avoided in this type of case, where there is much overlapping of clinical and laboratory findings and where hypercalcemia is the only constant feature, it is obvious that all possible diagnostic procedures should be undertaken at the outset.

### SUMMARY

A case of multiple myeloma with marked hypercalcemia and normal parathyroid glands is reported.

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### A CASE OF CAVERNOUS SINUS THROMBOPHLEBITIS SUCCESSFULLY TREATED BY COMBINED ANTICOAGULANT AND CHEMOTHERAPY\*

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IN a review of the world's literature up to 1936 Cavenagh<sup>1</sup> could find only a few reported recoveries from septic cavernous sinus thrombophlebitis. The septic type as described by Grove<sup>2</sup> is that in which the thrombosis reaches the cavernous sinus by way of its afferent vessels. With the advent of the sulfonamides six other instances of recovery have been recorded.<sup>3, 4, 5, 6</sup> Recently Nicholson and Anderson<sup>7</sup> reported another case successfully treated by penicillin.

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From the Medical Service, City Hospital. Anticoagulants were supplied by Abbott.

The case to be reported is of interest not only because of the recovery, but because it was successfully treated by a combination of sulfonamides and anti-coagulants.

### CASE REPORT

The patient was a married white woman 26 years old, who was admitted to the medical wards of City Hospital December 12, 1943 at 9:30 p.m. She was confused, noisy and disoriented. There was a marked swelling and protrusion of the right eye ball with pronounced inflammation of the conjunctiva. The throat was red. There was impaired resonance at the base of the right lung. The temperature was 106° F., pulse 132, respirations 40. The extremities showed no edema. The neck was flaccid and the Kernig, Babinski and Oppenheim reflexes were normal. The history obtained from a relative was that the patient worked as a chamber maid and had been treated for gonorrhea and syphilis at Bellevue hospital during the past year. For the past five weeks she had complained of pain on urination and itching "inside." There was nocturia 5 to 6 times a night. The ankles were swollen at night and normal in the morning. One month previously she had had an abscess of the right ear, and had had occasional pain and discharge of pus from the ear since that time. For the past two weeks she had a non-productive cough. Two days previously she complained of generalized aching. On December 11, 1943, the day before admission, she had a shaking chill, fever and vomiting. She was delirious and staggered as though she were drunk. The patient thrashed about in bed that night with continued chills, headache and photophobia.

A tentative diagnosis of cavernous sinus thrombosis was made with nephritis, meningitis, and brain tumor or abscess to be ruled out. The cerebrospinal fluid pressure was 257 mm., the cell count 5, Pandy reaction negative, sugar negative. Four grams of sulfadiazine were given intravenously in 75 c.c. distilled water and three grams sulfadiazine with bicarbonate were given by mouth, to be followed in four hours by two grams, with one gram every four hours thereafter. The urine contained a large amount of albumin (four plus) and many casts. The leukocyte count was 31,700 with 92 per cent polymorphonuclears. Early next day she was seen in consultation by the Eye, Ear, Nose and Throat, and Neurological Services. The right eye was painful and red with marked edema of the upper lid. The eye was nearly closed, and there was pronounced exophthalmos. The fundus showed enlarged veins, but no hemorrhage or choked disk. The diagnosis of cavernous sinus thrombosis was made by the ophthalmologist and the neurologist. Chemotherapy and possible jugular vein ligation were advised. The laryngologist was not sure of the diagnosis and thought there might be a right ethmoiditis with a ruptured anterior cell and an orbital abscess. He advised an external operation.

Cavernous sinus thrombosis was regarded as probable and combined anticoagulant and chemotherapy were instituted. One 10 c.c. vial of heparin was added to 500 c.c. saline infusion and administered at the rate of 20 drops a minute. The coagulation time was kept at three times normal. Sulfadiazine was continued by mouth as indicated above. During the first 24 hours in the hospital it was almost impossible to keep the patient quiet in spite of heavy sedation. Restraint was necessary while the infusion was being given until 6 c.c. of paraldehyde were injected intravenously when the patient fell asleep. Cultures of the spinal fluid and blood showed no growth. The blood non-protein nitrogen was 26 mg., sugar 100. On December 15 the temperature was 103, pulse 112, respirations 32. She was more rational and less noisy. Definite diplopia was noticed on this day. By this time 90,000 units of heparin had been administered and the veins were becoming thrombosed. It was therefore decided to try to continue the infusion through the sternum. A sternal puncture was done and the infusion was run in through the sternum at the rate of 20 drops per minute. She

now became increasingly restless, and dicumarol by mouth, 300 mg., was started with the intention of discontinuing the infusion soon. On the next day 200 mg. dicumarol were given. She was getting a bed sore and had great discomfort from the sternal infusion. It became imperative to turn her and discontinue the heparin. On the next day, December 18, the prothrombin level was 40 seconds, well within the therapeutic range so that the infusion was discontinued. Examination at this time showed evidence of consolidation in the middle of the left lung, confirmed by roentgen-ray. Roentgen-ray of the sinuses showed marked clouding of the anterior ethmoidal cells with obliteration of all the cells.

Since the laryngologists still believed an ethmoidal abscess was present it was decided to subject her to an operation. Under pentothal anesthesia an incision was made externally just below the right eye brow. The periosteum was separated but no pus, fistula or sequestrum could be found. The diagnosis of cavernous sinus thrombosis was therefore confirmed. She improved slowly and although penicillin had been obtained, it was decided to continue the sulfadiazine. The dicumarol had been continued in 100 mg. doses, sufficient to keep the prothrombin time prolonged to twice normal. On December 22, her temperature was 99, white blood cells 7,700. The following day chemotherapy was discontinued but dicumarol was kept up. On December 29 there was slight improvement of the exophthalmos and edema. The diplopia was also improving. Dicumarol was now discontinued. She continued to improve and was discharged as cured.

#### DISCUSSION

This case presents several unusual features which are worthy of further comment. The recovery of the patient is of course the most important and is due entirely to the new methods of chemotherapy. The differential diagnosis is interesting and the operation with its negative findings definitely helped in establishing the correct diagnosis. Worthy of further comment is also the difficulty of securing sedation of a patient with this condition. After a large variety of sedatives was tried it was found that intravenous paraldehyde was the most potent. The sternal route for infusion is of great value when no more veins are available but its use is also attended with a certain amount of pain and discomfort.

In this case sulfa drugs were used rather than penicillin mainly because penicillin was not available at the time of the illness. By the time the penicillin was obtained it was not necessary to use it. If both drugs had been freely available we would have used the penicillin because it acts not only on streptococci, but on staphylococci as well. Another reason for preferring penicillin in this case was the possibility of kidney damage in this patient.

The purpose of the anticoagulants was to prevent further extension of the thrombus. For immediate effect heparin is the drug of choice, as dicumarol does not exert an effect until 48 hours after administration. However, considering the fact that heparin must be given continuously by vein, dicumarol is the eventual drug of choice, for maintenance purposes.

#### SUMMARY

A case of cavernous sinus thrombophlebitis occurring in a 26 year old woman was successfully treated by combined anticoagulant and chemotherapy.

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## MASSIVE DERMOID CYST OF THE MEDIASTINUM, WITH REPORT OF A CASE\*

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MEDIASTINAL dermoid cysts are extremely rare. In 1928 Kerr and Warfield<sup>1</sup> computed the total number at 138, and some of these may not have been genuine intrathoracic dermoids. In June 1944 Rusby<sup>2</sup> published an excellent exhaustive review of dermoid cysts and teratoma of the mediastinum. Including the six he reported, he had traced 245 well authenticated cases up to 1939. A few additional cases have been published in the English and American literature since that time.<sup>3, 4, 5, 6, 7</sup> The rarity of the abnormality may be attested to by the fact that in 252,653 admissions to Philadelphia General Hospital from 1935 to 1944 inclusive, only one other case was diagnosed as intrathoracic dermoid cyst. This was in an infant five months old. The patient was operated on at the age of 15 months and the cyst was successfully removed.

The case presented here is reported not only because of the rarity of the condition, but because it also offers an opportunity to consider the interesting clinical problems encountered in the diagnosis and treatment of intrathoracic neoplasms in general, and dermoid cysts in particular.

Dermoid cysts may remain small, or may grow rapidly in adolescence or early adult life. They usually remain dormant until the third or fourth decade, when they begin to enlarge and produce pressure symptoms.

*Symptoms and Physical Signs.* The predominant symptoms depend upon the size of the mass and the amount of pressure it exerts on contiguous structures. There is usually cough, dyspnea and chest pain. The cough and dyspnea are often worse in the recumbent posture. This was noticed in our patient. The pain may be limited to a well localized area of the chest or it may be widespread.

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From the Wards of the Philadelphia General Hospital.

It is frequently pleural in origin, and at times may be quite intense. Less frequently hemoptysis may occur.

The physical signs also depend upon the size of the tumor, and on its influence upon the adjacent mediastinal organs. Thus one may encounter an upper or a lower mediastinal syndrome, or physical signs that may resemble any of the following conditions from which dermoid cyst must be differentiated. These are: (1) Tuberculosis; (2) pleural effusion or empyema; (3) lung abscess, bronchiectasis, pneumonitis; (4) mediastinal tumor, carcinoma, sarcoma, Boeck's sar-

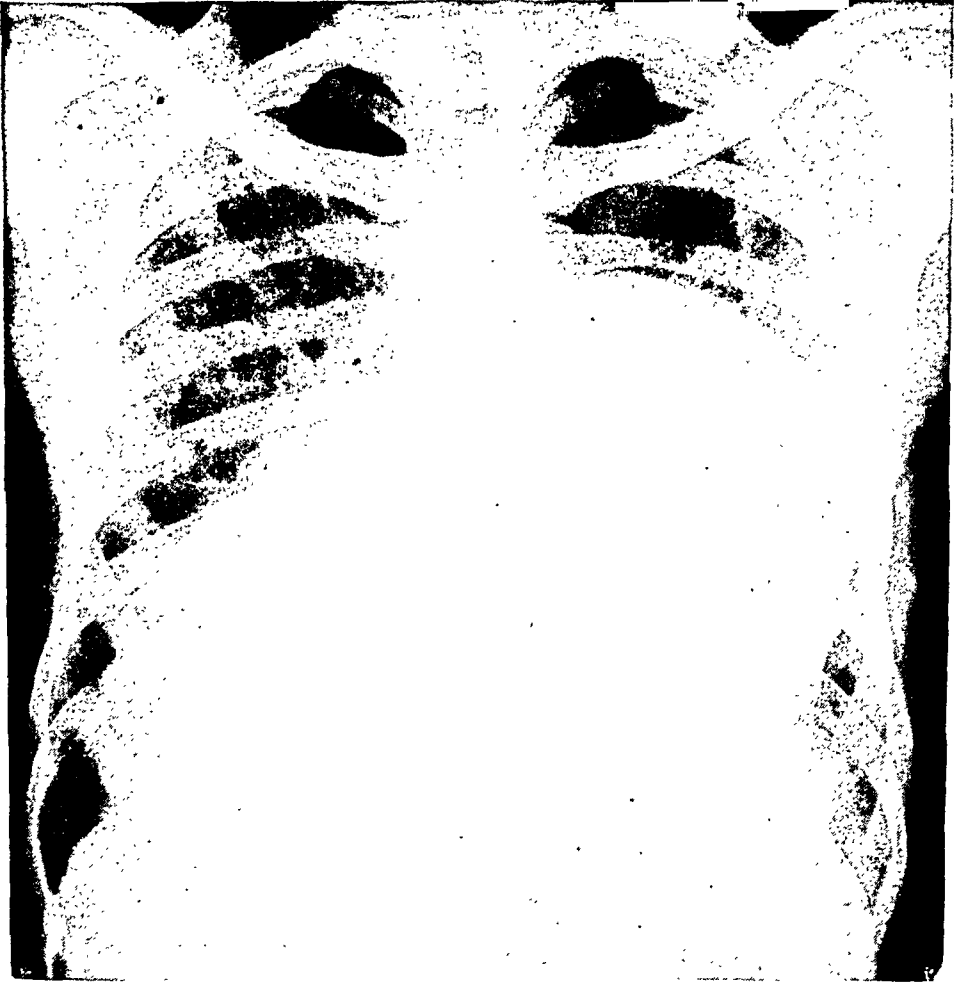


FIG. 1. Roentgenogram of chest Aug. 15, before aspiration.

coid, gumma, thymoma, leukemia, Hodgkin's disease; (5) pericarditis, pericardial effusion; (6) aortic aneurysm. The differential diagnosis can only be made or at least suggested by thorough radiological studies. Infrequently the expectoration of hair establishes the diagnosis. Rarely hair may be aspirated during diagnostic puncture, as happened with our patient. Aspiration should only be done after a thorough study of the patient. All observers emphasize the considerable risk involved in performing diagnostic paracentesis.<sup>2, 8, 9</sup>

*Treatment.* There is only one method of treatment, namely operation, and this should be done when disquieting symptoms occur. Wherever possible the

cyst should be removed intact.<sup>2, 8, 9, 10, 11, 12</sup> This, however, is at times difficult or impossible when one of the following complications is present: (1) Rapid progressive increase in size of the cyst; (2) the presence of a cyst-bronchial communication; (3) rupture of the cyst into adjoining structures; (4) the presence of adhesions to surrounding structures (great vessels, pericardium, pleura, etc.); (5) the presence of infection in the cyst; (6) the presence of malignancy.

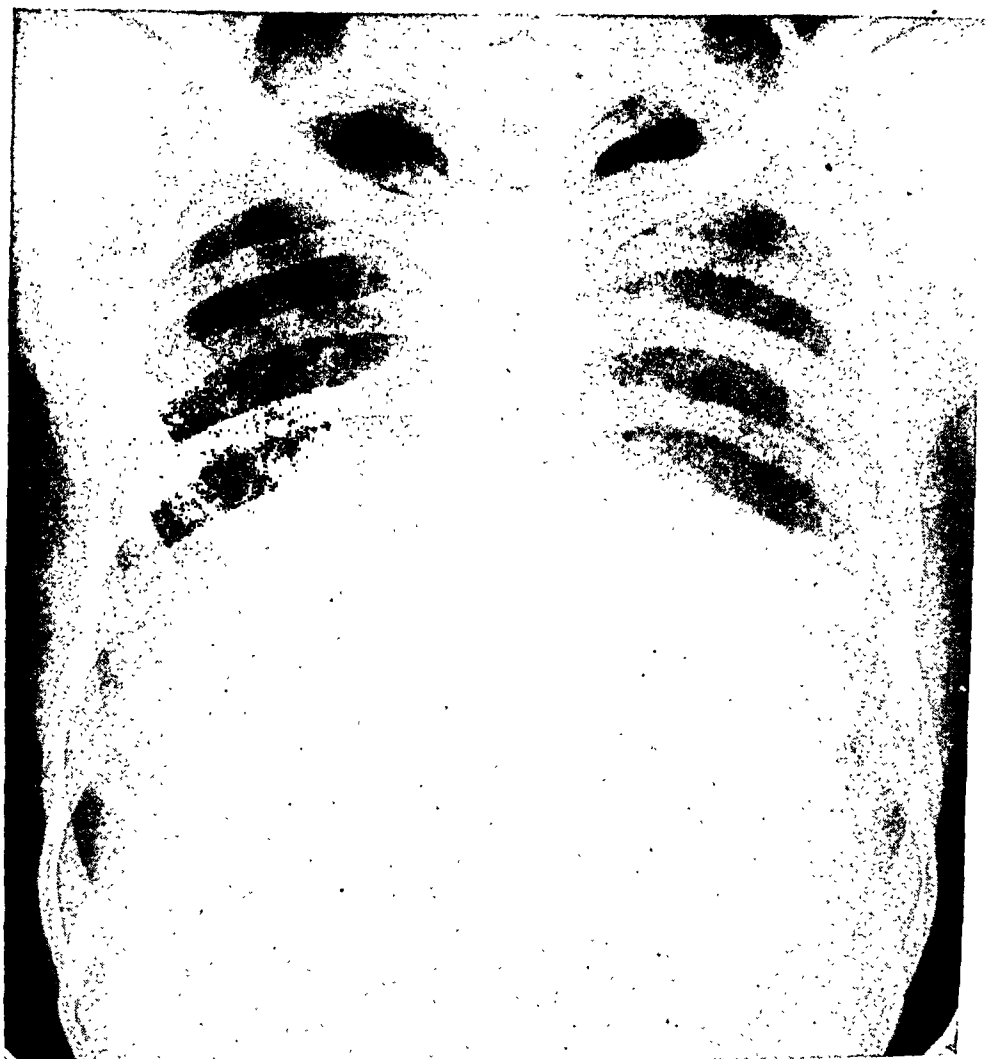


FIG. 2. Roentgenogram of chest, Aug. 16, following aspiration.

Certain complications such as rupture of the cyst into adjoining structures, formation of a cyst-bronchial fistula, infection of the remaining portion of a partially removed cyst, may occur during or because of the operation. When such complications occur, their management becomes an important problem.

The solid teratomata are more apt to become malignant and the dermoid cysts more frequently become infected.<sup>13</sup> Rapid growth may be provoked by the occurrence of an intercurrent infection.<sup>2, 9</sup> The onset of infection in a cyst may at times be sudden, dramatic and ominous. If a cyst communicates with a bronchus large quantities of pus may be expectorated. A number of cases have

been reported in which rupture of an infected cyst into the pleural cavity produced the clinical picture of the chronic empyema.<sup>3, 4, 7</sup>

The case here reported presented practically all of the symptoms and signs and many of the complications above mentioned.

#### CASE REPORT

C. A., colored male, aged 33, was admitted to the medical service of Dr. S. A. Loewenberg on Aug. 7, 1944, complaining of soreness in the chest and shortness of breath.

*History:* For about a year prior to his admission the patient noticed that he was becoming short of breath upon exertion and on climbing stairs. At the same time he

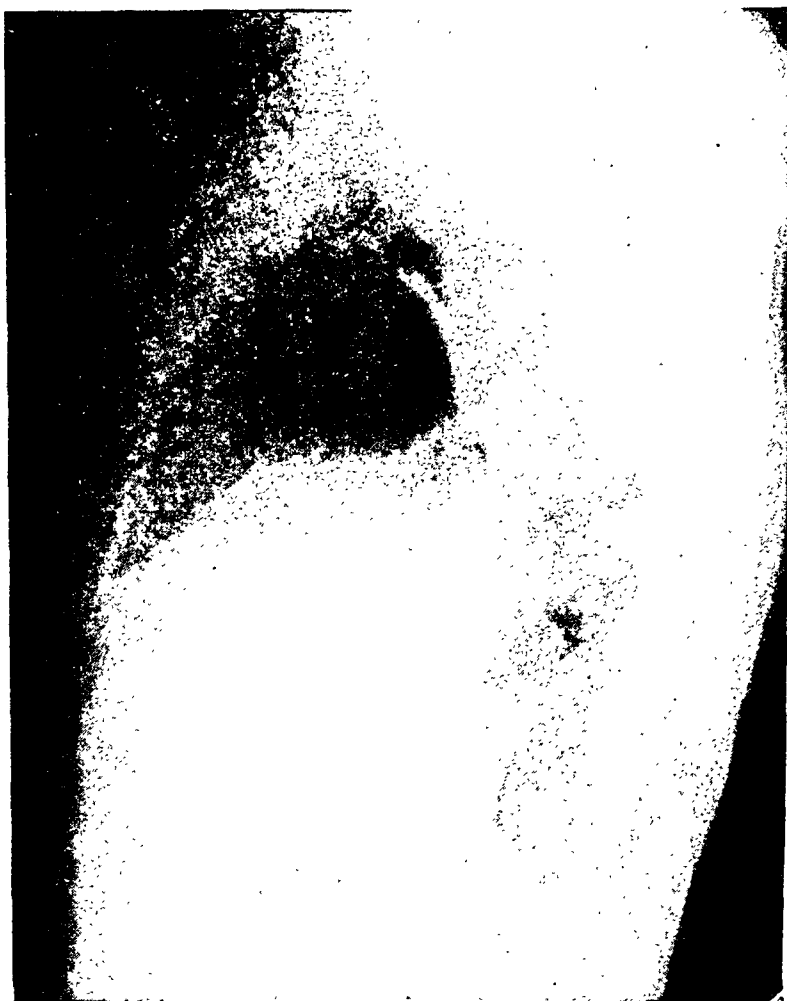


FIG. 3. Same as in figure 2, lateral view.

also noted a dull pain in his left chest that radiated to the neck. This was relieved by lying on the right side. These symptoms became progressively worse during that year, and on admission were accompanied by a cough and whitish yellow expectoration. Despite these complaints he continued his occupation as a manual laborer until three days prior to admission. About two weeks before this his feet began to swell, and



he developed nearly constant nausea. A physician who saw the patient prescribed digitalis.

*Physical Examination:* On examination the patient was obviously sick, and very much dyspneic in the recumbent position. The temperature was 99.0° F, the pulse rate 130 and the respiratory rate 35 per minute. His blood pressure was 96 mm. Hg systolic and 84 mm. diastolic. The respiratory movements were decreased over the entire chest. There was percussion dullness anteriorly and posteriorly over the whole left chest. On the right side dullness was noted in a triangular area from the second

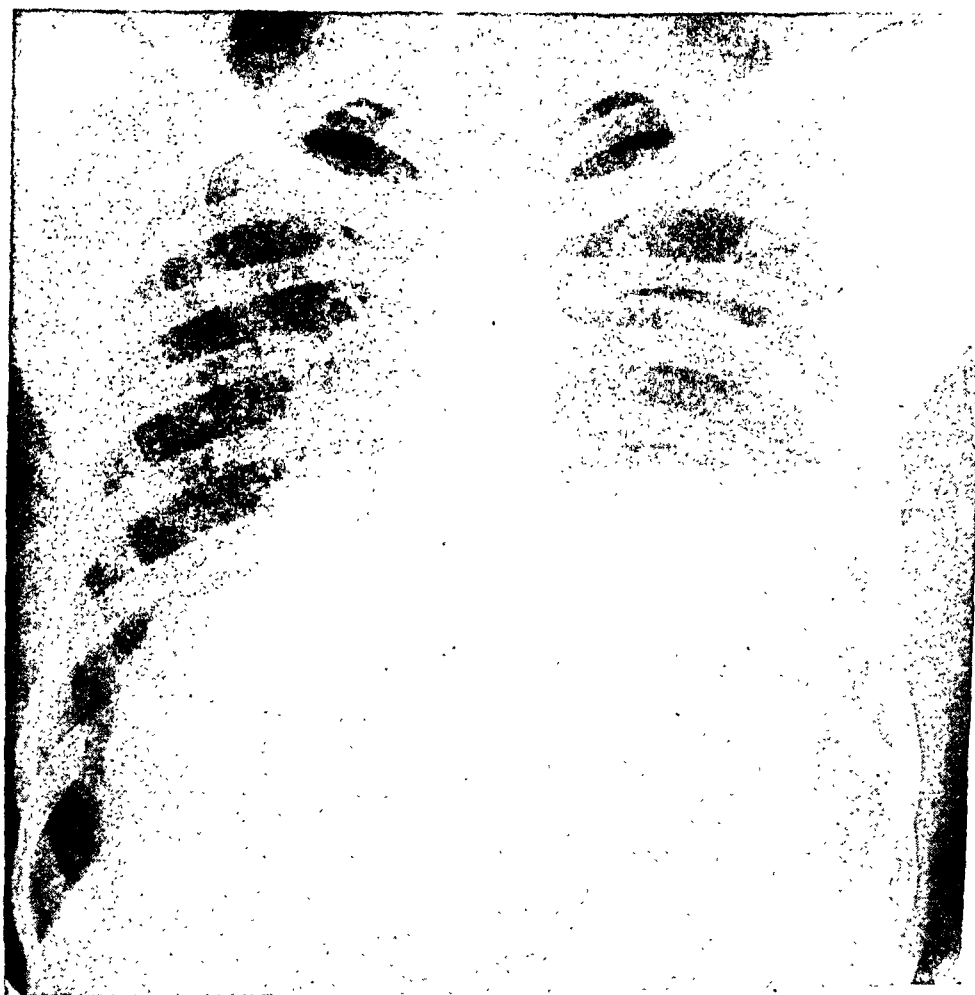


FIG. 4. Roentgenogram of chest Aug. 22, showing air and fluid level in the cyst.

costochondral junction to the sixth rib in the anterior axillary line. Breath sounds were decreased anteriorly and posteriorly over both sides of the chest. Friction rubs were heard readily over the entire left chest, over the right lower chest anteriorly, and in the right axilla.

The area of cardiac dullness extended in the fifth intercostal space from the left anterior axillary line to the right anterior axillary line. The heart sounds were heard most distinctly 10 cm. to the right of the midsternal line in the fifth intercostal space; no murmurs were audible. The liver was palpable two fingers'-breadth below the right costal margin. There was some ankle edema. The circulation time performed with 20 per cent calcium gluconate was 13 seconds. The following diagnoses were entertained: (1) Pericardial effusion with bilateral fibrinous pleurisy (rheumatic or

tuberculous); (2) atelectasis of right lower lobe; (3) mediastinal tumor; (4) aortic aneurysm.

The day after admission the patient had his first frank hemoptysis. A chest film taken on Aug. 8, 1944 revealed a large shadow in the left chest, continuous with or displacing the cardiac shadow to the right. No definite diagnosis was ventured, and fluoroscopy was suggested. On Aug. 15, 1944 fluoroscopy and a repeated roentgenogram (figure 1) were performed, but the interpretation was again uncertain. The possibility of pericardial effusion was suggested. On Aug. 16, 1944 thoracentesis was

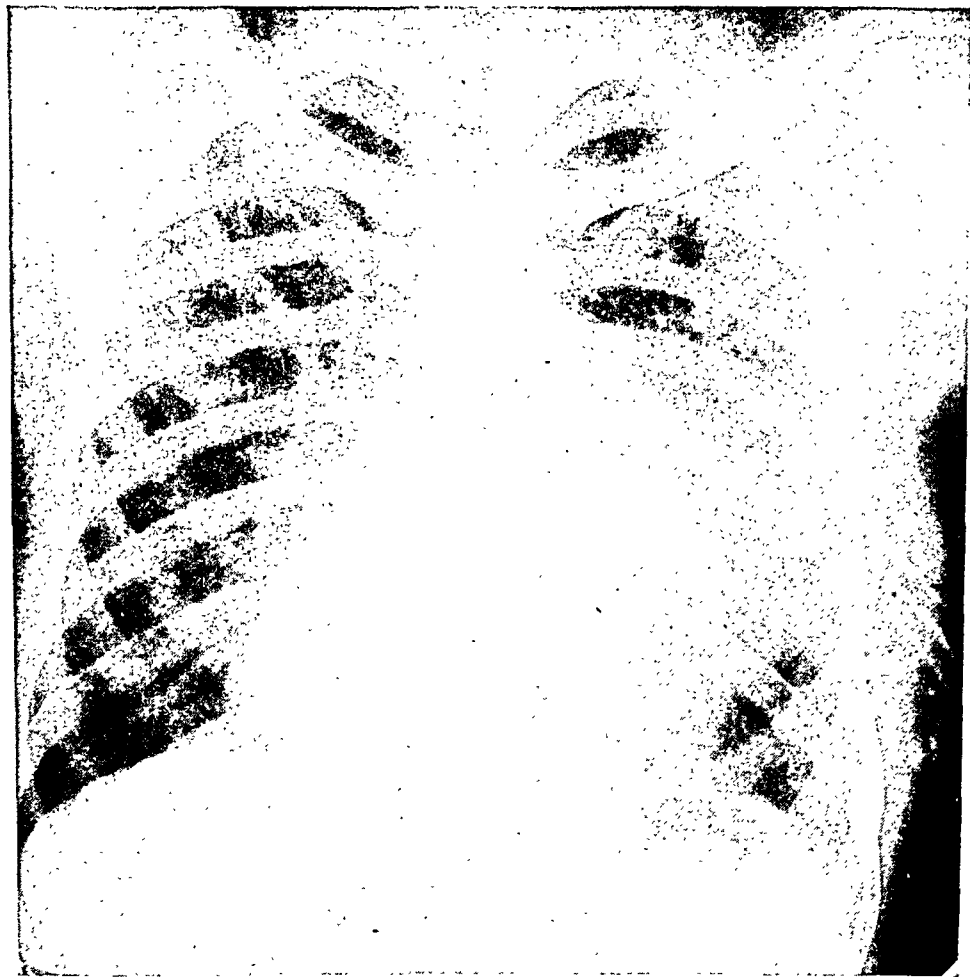


FIG. 5. Roentgenogram of chest Dec. 4, showing improvement.

performed. The needle was inserted in the left fifth intercostal space in the anterior axillary line, 600 c.c. of grayish brown caseous material were removed, and 300 c.c. of air injected. The roentgenologist then suggested the diagnosis of large dermoid cyst of the anterior mediastinum (figures 2 and 3). The fluid removed by thoracentesis was examined in the laboratory, and reported as pure pus that produced no growth on culture and was negative for acid-fast bacilli. On the roentgenogram taken on Aug. 22, 1944 a distinct air and fluid level in the cyst was visible (figure 4).

On Sept. 5, 1944, upon attempt at pericardial puncture in the left fifth interspace, 120 c.c. of "pea soup" material were aspirated. This contained particles of caseous material and several hairs. The diagnosis of mediastinal dermoid cyst was thus confirmed.

Two weeks later roentgenographic study revealed refilling of the cyst. At the same time the patient continued to have a septic temperature, dyspnea became more disturbing, and cyanosis was more apparent. A previously noted hepatomegaly became increasingly more marked. The patient was transferred to the surgical service of Dr. William T. Lemmon for surgical treatment of the cyst.

Operation under continuous spinal anesthesia and intratracheal anesthesia was performed by Dr. Lemmon on Sept. 9, 1944. After resection of the sixth left rib the cyst wall was exposed and about 30 oz. of thick, almost creamy material with debris



FIG. 6. Final roentgenogram showing marked improvement.

was aspirated. In addition a basin 8" in diameter by 3" high was almost filled with cheesy grayish-green material containing many hairs. It was then noted that the cyst was adherent to and continuous with the pericardium, extending from the second rib on the left down to the diaphragm. The left lung was compressed upward, and the heart occupied the right chest. Complete removal of the cyst seemed to offer far too great a surgical risk. The interior wall of the cyst was then fulgurated with electric cauterizer and the cyst wall closed.

After a few stormy days, gradual improvement in a desperately ill patient became apparent. A probable pneumonitis was treated with sulfadiazine three weeks post-operatively. Roentgenogram on Oct. 30, 1944 revealed reaccumulation of fluid in the cyst. In view of the reaccumulation, the persistent fever, and the profuse purulent

drainage, a second operation was performed on Nov. 16, 1944. When the cyst was opened about 1000 c.c. of creamy fluid were removed, including some sebaceous material and hair. An exhaustive attempt was made by Dr. Lemmon to destroy the entire cavity wall by desiccation, for removal of the cyst seemed technically almost impossible. Tube drains were inserted, and the cavity was irrigated daily. Marked improvement was seen on the roentgenogram taken on Dec. 4, 1944 (figure 5). The patient was discharged in excellent condition on Jan. 8, 1945, with two drainage tubes in a small remaining sinus. He has continued to return for irrigation once or twice a week,

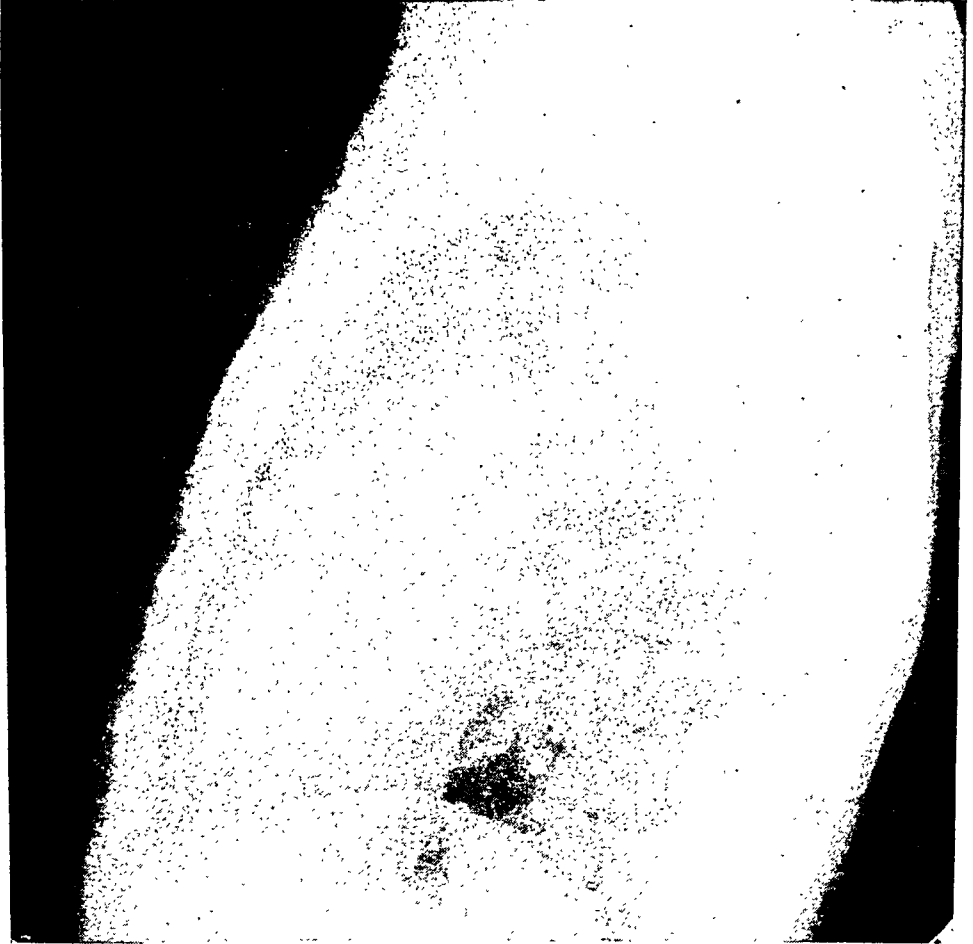


FIG. 7. Same as in figure 6, lateral view.

and when last examined by roentgenogram (figures 6 and 7) he was much improved. All tubes were out, though a very small sinus remained.

*Laboratory Data.* An electrocardiogram taken on Aug. 8, 1944 was practically normal, though there was some flattening of the T-waves in the CR leads. One month later definite changes had occurred. The T-waves were now inverted in Leads I, II, CR<sub>1</sub> and CR<sub>5</sub>, suggesting some myocardial involvement. On Sept. 9, 1944 the electrocardiogram was about the same, and it was suggested that the massive extracardiac disease might be responsible for the electrocardiographic changes.

Some of the pertinent laboratory studies are summarized in the accompanying table.

TABLE I

|                                                      | 8-10-44                      | 9-29-44                      | 10-3-44           | 10-20-44                     | 10-27-44          | 11-2-44    | 11-11-44          | 11-17-44 | 12-18-44          |
|------------------------------------------------------|------------------------------|------------------------------|-------------------|------------------------------|-------------------|------------|-------------------|----------|-------------------|
| Blood count<br>Hb.<br>R.B.C.<br>W.B.C.               | 11 gm.<br>3,120,000<br>4,200 | 12 gm.<br>4,300,000<br>6,200 |                   | 11 gm.<br>3,170,000<br>7,500 |                   |            |                   | 11.8 gm. |                   |
| Cholesterol,<br>mg. % and<br>esters                  |                              |                              |                   |                              |                   | 144<br>71% |                   |          |                   |
| Blood urea N,<br>mg. %                               | 22                           |                              |                   |                              |                   |            |                   |          |                   |
| Blood sugar,<br>mg. %                                | 82                           |                              |                   |                              |                   |            |                   |          |                   |
| Serum proteins<br>Total %<br>Albumin %<br>Globulin % |                              | 5.9<br>3.1<br>2.8            | 6.7<br>3.4<br>3.3 | 6.9<br>3.0<br>3.9            | 7.4<br>3.3<br>4.1 |            | 8.1<br>3.4<br>4.7 |          | 8.2<br>4.0<br>4.2 |
| Blood Wassermann                                     | Negative                     |                              |                   |                              |                   |            |                   |          |                   |
| Blood chloride<br>M.E.Q.,<br>mg. %                   |                              |                              |                   | 573                          |                   |            |                   |          |                   |

## COMMENT

Viewed in retrospect, it is easy to attribute the symptoms and physical findings to sudden increase in size in a large dermoid cyst of the mediastinum. An intercurrent infection could have precipitated the infection within the cyst itself. The displacement of the heart and the pressure on the mediastinal structures produced the dyspnea, pain, cough and hemoptysis.

When first seen, however, the differential diagnosis was rather difficult. Pericardial disease was considered a strong possibility, and the cyanosis, hepatomegaly, and peripheral edema helped substantiate this impression. The normal circulation time, despite the dyspnea, cyanosis and edema, is further confirmation of the reports emphasizing the value of measuring the velocity of blood flow in the differentiation of puzzling pulmonary or cardiac conditions.<sup>14, 15</sup>

The changes in the serum proteins are interesting, and may possibly bear a direct relation to the dermoid cyst. Following the first operation, it was noted that the patient's hepatomegaly was increased and that definite ascites had developed. A fall in the serum albumin with reversal of the albumin globulin ratio was considered as a possible causative factor. The administration of a high protein diet helped overcome the ascites. It is conceivable that the protein loss resulting from the removal of tremendous quantities of cheesy caseous material, detritus and pus, could have contributed to the albumin-globulin reversal and the ascites.

It is at present difficult to predict whether or not this patient will remain well. If any of the secreting cyst wall remained, the cyst may eventually refill. It is generally agreed by all surgeons with experience in this field, that removal

of the intact cyst in toto is the procedure of preference. However, a number of complications may, as in this case, make it difficult or impossible. Others have reported the use of chemical cauterization when surgical removal of the cyst in toto was not possible.<sup>4</sup>

### CONCLUSION

A case of massive dermoid cyst of the mediastinum is presented in a 33 year old colored male.

The symptoms and differential diagnosis are discussed. The roentgen-ray diagnosis was confirmed by the aspiration of hair upon thoracentesis.

At operation it was found impossible safely to remove the entire cyst, and the cyst contents were evacuated and the secreting surface extensively cauterized in two stages.

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## EDITORIAL

### *ACUTE HEMOLYTIC ANEMIA FOLLOWING ADMINISTRATION OF SULFADIAZINE*

THE abrupt appearance of a severe anemia of hemolytic type has been generally recognized as an occasional complication of sulfonamide therapy since the condition was first reported by Harvey and Janeway<sup>1</sup> in 1937. Such reactions were relatively common with sulfanilamide, occurring in 1.8 per cent of the cases according to Long et al.<sup>2</sup> Similar reactions have occurred less frequently following sulfapyridine and sulfathiazole. Sulfadiazine has been regarded as relatively safe in this respect, but several cases of such an anemia have been reported. We have found reports of 10 cases in which acute hemolytic anemia appeared in patients during or shortly after the administration of sulfadiazine and in which the drug may have caused or participated in the production of the anemia.<sup>3, 4, 5, 6, 7, 8, 9</sup> In some of these cases, however, other causes may have been operative.

The gradual development of a mild or moderate degree of anemia is not uncommon during the administration of the sulfonamides, it is usually of relatively minor significance and does not necessitate stopping the use of the drug. The acute cases, on the other hand, develop abruptly, often within three to seven days after the drug is started. Destruction of the red cells progresses with great rapidity. There is hemoglobinemia and hemoglobinuria, with the development of jaundice and the other usual manifestations of an hemolytic anemia. Hemolysis may continue for several days after detectable amounts of sulfonamide have disappeared from the blood. A hyperleukocytosis is common. Such a reaction is a grave danger to life unless it is promptly recognized, the drug immediately stopped and prompt treatment instituted. The mortality has been estimated at from 5 to 10 per cent.

The mechanism by which the cells are destroyed has been studied fairly

<sup>1</sup> HARVEY, A. M., and JANEWAY, C. A.: The development of acute hemolytic anemia during the administration of sulfanilamide, *Jr. Am. Med. Assoc.*, 1937, cix, 12.

<sup>2</sup> LONG, P. H., HAVILAND, J. W., EDWARDS, L. B., and BLISS, E. A.: The toxic manifestations of sulfanilamide and its derivatives, *Jr. Am. Med. Assoc.*, 1940, cxv, 364.

<sup>3</sup> BOYER, N. H.: Acute hemolytic anemia following sulfadiazine; report of a case, *New England Jr. Med.*, 1943, ccxxviii, 566.

<sup>4</sup> DAMESHEK, WILLIAM: Cold hemagglutinins in acute hemolytic reactions, in association with sulfonamide medication and infection, *Jr. Am. Med. Assoc.*, 1943, cxiii, 77.

<sup>5</sup> DOWLING, H. F., and LEPPER, M. H.: Toxic reactions following therapy with sulfapyridine, sulfathiazole and sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1190.

<sup>6</sup> LAYNE, J. A., and SCHEMM, F. R.: Acute macrocytic anemia following administration of sulfadiazine, *Jr. Lab. and Clin. Med.*, 1944, xxix, 347.

<sup>7</sup> DONALD, D., and WUNSCH, R. E.: Acute hemolytic anemia with toxic hepatitis caused by sulfadiazine; report of a case, *Ann. Int. Med.*, 1944, xxi, 709.

<sup>8</sup> FINLAND, M., PETERSON, O. L., ALLEN, H. E., SAMPER, B. A., and BARNES, M. W.: Cold agglutinins. II. Cold isohemagglutinins in primary atypical pneumonia of unknown etiology with a note on the occurrence of hemolytic anemia in these cases, *Jr. Clin. Invest.*, 1945, xxiv, 458.

<sup>9</sup> ROSS, J. F., and PAEGEL, B. L.: Acute hemolytic anemia and hemoglobinuria following sulfadiazine medication, *Blood*, 1946, i, 189.

extensively without arriving at any final conclusions. Attempts to demonstrate hemolysins by *in vitro* tests have been unsuccessful or unconvincing. The cells of the patient *in vitro* are not hemolyzed by sulfonamides in concentrations far higher than those that occur in the blood. In many cases, if examined at the height of the reaction, the blood has contained large numbers of spherocytes. An increase in the average thickness of the cells has been demonstrated, and, as might be anticipated, there is an increased fragility of the red cells in hypotonic salt solution. Such observations, however, probably prove merely that the cells have been injured and that their destruction is imminent, but do not indicate the nature or mechanism of the injury.

In some cases sulfonamides had previously been administered. The abruptness of the onset and the relatively small amounts which may suffice to precipitate the anemia suggest that this is a manifestation of hypersensitivity to the drug.

In a substantial number of cases which have been studied as to this point, including a majority of those reported after sulfadiazine, cold agglutinins (autoagglutinins) have been demonstrated in the serum, often in high concentration. Some of these patients had primary atypical pneumonia and several had milder respiratory infections which may have been caused by the same agent. Furthermore, Finland et al.<sup>8</sup> have reported the occurrence of acute hemolytic anemia in cases of primary atypical pneumonia with cold agglutinins in the serum, who had received no sulfonamides prior to the appearance of the anemia. In one such case<sup>8</sup> sulfadiazine was administered after the anemia appeared without deleterious effect; in fact, the anemia improved during the treatment. Such observations raise the questions as to whether the anemia in these cases was due to the sulfadiazine at all, and whether the cold agglutinins may have been in some way responsible.

There has been much speculation as to how such agglutinins might cause hemolysis. No associated hemolytic activity has been demonstrated *in vitro*, and the Donath-Landsteiner test has been negative when tried. *In vitro* the agglutination is usually demonstrable only at low temperatures and breaks up when the preparations are raised to body temperatures or even to room temperature. If the titer is very high, however, some degree of agglutination may persist for a time, even at 37° C. In such cases it is conceivable that cells circulating through cold extremities might be agglutinated *in vivo*. Such agglutinated cells may be abnormally susceptible to mechanical trauma in the circulation. The agglutinated cells would not pass through the capillaries, or only with great difficulty, and a condition of "erythrosthosis" would be produced in the tissues. Ham and Castle<sup>10</sup> have advanced evidence that such erythrosthosis, experimentally produced, damages the red cells,

<sup>10</sup> HAM, T. H., and CASTLE, W. B.: Relation of increased hypotonic fragility and of erythrosthosis to the mechanism of hemolysis in certain anemias, *Trans. Assoc. Am. Phys.*, 1940, 1v, 127.



causing spherocytosis, increased fragility in hypotonic salt solution, and hemolysis in vivo. The evidence available is not sufficient to determine these points.

Cold agglutinins have been reported in cases of acute hemolytic anemia in which there was no reason to suspect infection with the agent of primary atypical pneumonia. Since there is evidence that this agent may cause mild and probably subclinical infections,<sup>11</sup> it is at present impossible to exclude it absolutely as the cause of the cold agglutination in such cases of anemia. There are many cases of acute hemolytic anemia in which cold agglutinins are not demonstrable.

That sulfadiazine may cause severe acute hemolytic anemia independently of primary atypical pneumonia seems amply proved by the case recently reported by Ross and Paegel.<sup>9</sup> A child of four, who had received sulfadiazine twice before, was again given this drug because of an acute tonsillitis and pharyngitis. Three doses of 0.25 gm. were given, some of which was vomited. Within 18 hours after the first dose an unusually severe hemolytic anemia developed, from which she eventually recovered after massive transfusions. It was estimated that 70 per cent of the erythrocytes were destroyed within 36 hours. The blood showed marked spherocytosis, and the fragility of the red cells in hypotonic salt solution was increased, but no hemolysins or agglutinins of any sort could be demonstrated. It seems probable that in this case hypersensitiveness had developed and that the red cells were directly injured by the drug or by some metabolite of the drug.

Although patients with acute hemolytic anemia sometimes react severely to transfusions, the latter have been given repeatedly to patients with cold agglutinins in the blood without incident provided the blood is properly matched. It seems prudent to introduce the blood at body temperature in such cases, as advised by Dameshek and others, although there appears to be no direct proof of the necessity for this. It also seems advisable to protect patients with cold agglutinins from chilling, since Ham<sup>12</sup> has produced hemoglobinemia by chilling the limb in such a case (with a negative Donath-Landsteiner reaction).

It is manifestly necessary carefully to observe all patients receiving sulfadiazine with reference to the blood, even though severe anemia seems to be a rare complication. Particular caution should probably be exercised in cases of primary atypical pneumonia or other diseases with cold agglutinins in the blood.

<sup>11</sup> Editorial: Primary atypical pneumonia, *Ann. Int. Med.*, 1946, xxiv, 727.

<sup>12</sup> Quoted by Finland, reference 8.

## REVIEWS

*Clinical Roentgenology of the Heart.* By JOHN B. SCHWEDEL, M.D. 380 pages; 26.5 × 20.5 cm. Paul B. Hoeber, Inc., New York. 1946. Price, \$12.00.

If this reviewer were to use but one word in describing this volume, it would be "excellent." Dr. Schwedel deserves considerable praise for having published this work, for it fills a vacancy of long standing in medical literature.

In the first four chapters, the author lists the various methods of study and measurement of the heart. He describes several means used to determine heart size, evaluating each method's good and bad points. He does not, unfortunately, indorse any one particular procedure, so that the reader is left inadvised as to what the most satisfactory method is.

The major portion of the volume is devoted to the roentgenological description of pathological chambers of the heart. The text is concise and extremely well illustrated by suitable case histories and film reproductions. A very helpful device, in the form of line drawings, has been adopted; these serve well to illustrate the pathological features of the films. It is regrettable, but the films as reproduced are positive ones.

That one would quarrel with Dr. Schwedel's theories as to cardiac enlargement is very unlikely; however, his views regarding the differentiation of acute pulmonary congestion from other pulmonary lesions are open to question.

The volume is made complete by the inclusion of diseases of the pericardium, the congenital cardiac anomalies and extra-cardiac lesions, causing displacement of the heart. The diagnostic points in regard to each abnormality are brief, but adequate.

Residents in departments of roentgenology will gain much from this reference book. It should be required reading. Likewise, the general practitioner will find it a satisfactory reference. The specialist in cardiology and roentgenology will find it a ready, though not exhaustive, volume for consultation.

D. J. B.

## BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Cosmetics and Dermatitis.* By LOUIS SCHWARTZ, M.D., and SAMUEL M. PECK, U. S. Public Health Service. 189 pages; 22 × 15 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$4.00.

*Motor Disorders in Nervous Diseases.* By ERNST HERZ, M.D., and TRACY J. PUTNAM, M.D. 184 pages; 24 × 16 cm. 1946. King's Crown Press, New York. Price, \$3.00.

*Diseases of the Adrenals.* By LOUIS J. SOFFER, M.D. 304 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price \$5.50.

*The Venous Pulse and Its Graphic Recording.* By FRANZ M. GROEDEL, M.D. 223 pages; 26 × 18.5 cm. 1946. Brooklyn Medical Press, New York. Price, \$5.50.

*Clinical Laboratory Diagnosis.* By SAMUEL A. LEVINSON, M.S., M.D., Ph.D., and ROBERT P. MACFATE, Ch.E., M.S., Ph.D. 971 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$10.00.

*Scientific, Medical and Technical Books.* Edited by R. R. HAWKINS. 1,114 pages; 28.5 × 21 cm. 1946. National Research Council, Washington, D. C. R. R. Bowker Company, distributors.

*Universidad de Antioquia.* By POSADA and NARANJO. 399 pages; 25 × 17 cm. 1945. Medellin, Colombia, S. A.

*Modern Management in Clinical Medicine.* By FREDERICK ALBRECHT, M.D. 1238 pages; 26 × 17.5 cm. 1946. Williams and Wilkins, Baltimore, Maryland. Price, \$10.00.

## COLLEGE NEWS NOTES

### THE JAMES D. BRUCE FUND

Dr. James D. Bruce, F.A.C.P., Ann Arbor, Michigan, Emeritus Vice President of the University of Michigan and Past President of The American College of Physicians, has made an initial gift of \$10,000.00 to the Endowment Fund of The American College of Physicians, the principal to be held intact and the income used for educational purposes. The donor has long had a primary interest in graduate and continuing medical education.

This initial gift by Dr. Bruce is intended for the establishment of a periodic Service Award in memory of the late Dr. Alfred Stengel, who, in the middle 20's, was responsible for widespread reorganization and reforms in the College, and who had a great influence on building the College as it is known today. Dr. Stengel's record stands out as one of great service to the College and to internal medicine, and thus our present Board of Regents will consider seriously the propriety of applying half of the Bruce Fund to a Memorial Service Award.

Dr. Bruce also suggested that the other half of the Fund be used in establishing a Lectureship in Preventive Medicine, and it is anticipated that a special committee appointed by the Board of Regents to take immediate steps to work out appropriate details, will name this "The James D. Bruce Lectureship in Preventive Medicine."

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### THE PHILADELPHIA SESSION OF THE COLLEGE

Never before, in the history of the College, has there been conducted a more successful, enthusiastic and valuable Session than the Twenty-seventh Annual Session in Philadelphia, May 13-17, 1946. Every committee and every institution strove to make this first postwar Session an outstanding occasion, scientifically and socially. Every feature of the Meeting appeared to be arranged in a superb manner; the President, Dr. Ernest E. Irons, selected speakers for the General Sessions and Morning Lectures, whose presentations met the anticipation of the members; the Panel Discussions were so popular that the facilities proved entirely inadequate; the Clinics at the hospitals, in most instances, were oversubscribed; the social features of the Meeting, including the Concert by the Orpheus Club, the Victory Convocation and the Banquet, were far above expectations. As a matter of fact, the grand ballroom of the Benjamin Franklin Hotel was inadequate to accommodate the large numbers who wished to attend the Concert, the Convocation and the Banquet.

The General Chairman, Dr. George Morris Piersol, displayed his usual inspiring leadership, which procured the ready coöperation of all committeemen and Philadelphia institutions.

Philadelphia's hotel and transportation accommodations were taxed to the utmost, and the College registers with deep regret the difficulties visiting physicians, in some instances, experienced in obtaining desired accommodations. It must be remembered, of course, that these conditions are nation wide, and that probably Philadelphia did as well or better than any other city could have done at this time.

An analysis of the registration shows that there were in attendance, 1528 member physicians, 1156 guest physicians, 485 senior medical students, 462 exhibitors, 23 guest non-physicians, and 358 visiting ladies, wives and daughters of members; total, 4012.

The Ladies' Entertainment Committee performed an outstanding service to the visiting women. The social events arranged by this Committee were received with delight and great appreciation. Altogether, the College feels deeply gratified with the Session.

## THE TWENTY-EIGHTH ANNUAL SESSION OF THE COLLEGE, 1947

On Friday, May 17, the Board of Regents chose Chicago for its 1947 meeting place, and appointed Dr. LeRoy H. Sloan, F.A.C.P., of Chicago, as the General Chairman. Plans are immediately being made for the selection of hotel headquarters, designation of dates, appointment of committees and the making of other arrangements. Announcements will be published in these pages from month to month. The program of General Sessions and Morning Lectures will be in charge of Dr. David P. Barr, President, New York City; local arrangements and the program of Clinics and Panel Discussions will be in charge of the General Chairman. Members are invited to send to the Executive Offices of the College suggestions and recommendations.

## NEW OFFICERS, REGENTS AND GOVERNORS OF THE COLLEGE

During the Philadelphia Annual Session of the College, at the Annual Business Meeting, Dr. David P. Barr, President-Elect, was inducted as President, and the following elections made:

President-Elect ..... Hugh J. Morgan, Nashville, Tenn.  
 First Vice President ..... James J. Waring, Denver, Colo.  
 Second Vice President ..... A. B. Brower, Dayton, Ohio  
 Third Vice President ..... T. Homer Coffen, Portland, Ore.

New Members, Board of Regents—*Term Expiring 1949*

Ernest E. Irons, Chicago, Ill.  
 William S. McCann, Rochester, N. Y.  
 T. Grier Miller, Philadelphia, Pa.  
 Charles F. Moffatt, Montreal, P. Q.  
 Charles F. Tenney, New York, N. Y.

## New Members, Board of Governors

*Term Expiring 1947*

Delivan A. MacGregor, Wheeling ..... WEST VIRGINIA  
 Arthur T. Henderson, Montreal ..... QUEBEC

*Term Expiring 1948*

E. Dice Lineberry, Birmingham ..... ALABAMA  
 Marion A. Blankenhorn, Cincinnati ..... OHIO  
 Karver L. Puestow, Madison ..... WISCONSIN

*Term Expiring 1949*

Leland P. Hawkins, Los Angeles ..... CALIFORNIA (Southern)  
 Ward Darley, Denver ..... COLORADO  
 Thomas P. Murdock, Meriden ..... CONNECTICUT  
 Wallace M. Yater, Washington ..... DISTRICT OF COLUMBIA  
 Cecil M. Jack, Decatur ..... ILLINOIS (Southern)  
 Robert M. Moore, Indianapolis ..... INDIANA  
 Harold H. Jones, Winfield ..... KANSAS  
 Chester S. Keefer, Boston ..... MASSACHUSETTS  
 Joseph D. McCarthy, Omaha ..... NEBRASKA  
 Edward C. Reifstein, Sr., Syracuse ..... NEW YORK (Western)  
 Wann Langston, Oklahoma City ..... OKLAHOMA  
 Edward L. Bortz, Philadelphia (Vice Chairman) ... PENNSYLVANIA (Eastern)  
 Roy R. Snowden, Pittsburgh ..... PENNSYLVANIA (Western)

|                                            |                                          |
|--------------------------------------------|------------------------------------------|
| John L. Calene, Aberdeen .....             | SOUTH DAKOTA                             |
| William C. Chaney, Memphis .....           | TENNESSEE                                |
| Louis E. Viko, Salt Lake City .....        | UTAH                                     |
| Harry L. Arnold, Sr., Honolulu .....       | HAWAII                                   |
| Herbert K. Detweiler, Toronto .....        | ONTARIO                                  |
| Francisco de P. Miranda, Mexico City ..... | MEXICO                                   |
| Gilbert M. Stevenson, Ancon .....          | REPUBLIC OF PANAMA and the<br>CANAL ZONE |

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SECOND INTER-AMERICAN CONGRESS OF CARDIOLOGY  
TO BE HELD IN MEXICO CITY

The Second Inter-American Congress of Cardiology will be held in Mexico City, October 6-12, 1946, under the Presidency of Dr. Ignacio Chavez, F.A.C.P.

The Congress will be conducted under the auspices of the American Heart Association, the Argentine Cardiological Society, the Cuban Cardiological Society and the Mexican Cardiological Society.

This will be the first continental meeting of cardiologists since the end of the War. Distinguished European cardiologists have been invited to attend as guests of honor.

The meeting place will be the National Institute of Cardiology, of Mexico, Calzada de la Piedad 300, Mexico, D. F.

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NEW LIFE MEMBERS OF THE COLLEGE

The College is gratified to announce the following additional Life Members, listed in the order of subscription:

Lt. Col. John William Shuman, Sr., F.A.C.P., Santa Monica, Calif.  
 Dr. James Johnston Waring, F.A.C.P., Denver, Colo.  
 Dr. John Wilfred MacIntosh, F.A.C.P., Halifax, N. S., Can.  
 Dr. Samuel Marshall Poindexter, F.A.C.P., Boise, Idaho

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POSTGRADUATE COURSES

TENTATIVE PRELIMINARY SCHEDULE, AUTUMN, 1946

| <i>Dates</i>     | <i>Subject Title</i>     | <i>Director</i>                               | <i>Location</i>   |
|------------------|--------------------------|-----------------------------------------------|-------------------|
| September 16-28. | Internal Medicine        | Dr. R. R. Snowden                             | Pittsburgh, Pa.   |
| September 23-28. | Psychosomatic Medicine   | Dr. Franklin Ebaugh                           | Denver, Colo.     |
| October 7-12.    | Clinical Neurology       | Dr. Bernard Alpers                            | Philadelphia, Pa. |
|                  | Internal Medicine*       | Dr. Homer Rush                                | Portland, Ore.    |
| October 14-19.   | Cardiovascular Disease   | Dr. Roscoe Miller                             | Chicago, Ill.     |
| October 21-26.   | Hematology               | Dr. Charles Doan                              | Columbus, Ohio    |
| October 28-      |                          |                                               |                   |
| November 9.      | Internal Medicine        | Dr. Wallace Yater                             | Washington, D. C. |
| November 4-9.    | Allergy                  | Dr. Robert Cooke                              | New York, N. Y.   |
|                  | Cardiology               | Dr. Paul White, and<br>Drs. Bland and Sprague | Boston, Mass.     |
| November 11-15.  | Tissue Growth and Tumors | Dr. E. L. Bortz and<br>Dr. Stanley Reimann    | Philadelphia, Pa. |
| November 11-16.  | Gastro-enterology        | Dr. Walter L. Palmer                          | Chicago, Ill.     |
| November 18-23.  | Internal Medicine*       | Dr. Joseph Hayman                             | Cleveland, Ohio   |
| November 25-30.  | Internal Medicine*       | Dr. J. C. Meakins                             | Montreal, Que.    |
| December 2-7.    | Chemotherapy             | Dr. W. Barry Wood, Jr.                        | St. Louis, Mo.    |
|                  | Cardiology               | Dr. Frank Wilson                              | Ann Arbor, Mich.  |

\* It is hoped that all courses in Internal Medicine may be expanded to include two weeks of instruction. Announcements will follow later.

Dr. Christopher C. Shaw, F.A.C.P., Wallingford, Pa., who assumed the office of Educational Director of the American College of Physicians on November 1, 1945, has resigned as of June 1, 1946; to become assistant medical director of the Medical Research Laboratories of Sharp and Dohme, Glenolden, Pa.

The Advisory Committee on Postgraduate Courses with the approval of the Board of Regents has adopted the following policy concerning the A.C.P. program of postgraduate courses and the GI Bill of Rights:

"The postgraduate courses sponsored by The American College of Physicians are organized primarily for Fellows and Associates of the College. Some non-members may be accommodated when facilities permit, but in the majority of courses, all places are taken by members.

"During the period of World War II, the College charged no tuition fee to any medical officer on active duty or on terminal leave. This courtesy was extended to members and non-members alike. With the termination of the war, and the increased demand for the College courses, our facilities have been taxed to the maximum, with the result that a much smaller number of non-members can be accommodated. In fact, facilities in some courses are inadequate for the member demand.

"The College will be unable to provide veteran medical officers, members or non-members of the College, the benefits of the amended GI Bill of Rights, through which the Veterans Administration would pay tuition fees of medical veterans pursuing its courses. The College has not the administrative machinery to comply with the various and intricate regulations through which collections must be made through the Veterans Administration.

"Furthermore, it is believed that the legislators who formulated the original training program for veterans did not have in mind the short one, two or three weeks courses, such as provided by this College. Fees for College courses are comparatively small; all such fees are turned over to the director or institution where a College course is given; the College underwrites all other expenses of promotion, advertising, printing and registration.

"The College regrets its inability, at this time, financially and administratively, to launch upon a program of training for medical veterans, through the Veterans Administration, but will accommodate as many as possible, who wish to register in the regular manner."

During the period of World War II, including the spring of 1946, the College charged no registration or tuition fee to medical officers on active duty or terminal leave attending its postgraduate courses. From one third to one half of registration in many postgraduate courses was composed of medical officers.

At a meeting of the Advisory Committee held on May 13, 1946, it was voted to discontinue this procedure as of July 1, 1946. The Advisory Committee plans to sponsor some 15 or more short refresher courses during the autumn months, beginning in September and running until the middle of December. The routine registration fee of \$20.00 per week to members of the College and \$40.00 per week to non-members will apply to all registrants, civilian or military, except in special courses where the tuition fees may be doubled for intensive instruction.

The Committee on Fellowships and Awards, with the approval of the Board of Regents, announces the following awards:

#### *Clinical Fellowships*

Dr. John Franklin, Cincinnati, Ohio—Internal Medicine—Johns Hopkins Hospital.  
Dr. Gordon S. Myers, Chestnut Hill, Mass.—Cardiology—Massachusetts General Hospital.

*Research Fellowships*

Dr. Charles P. Emerson, Jr., Boston, Mass.—Anemia—Thorndike Memorial, Boston City Hospital. (Circumstances have developed, preventing Dr. Emerson from accepting this award.)

Dr. Thomas S. Sappington, New Haven, Conn.—Nitrogen Metabolism—Graduate Hospital, University of Pennsylvania.

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Dr. Raymond Bernard Allen, F.A.C.P., Chicago, Dean of the University of Illinois College of Medicine since 1941, has recently been named president of the University of Washington, Seattle.

Since he is the first Fellow of the American College of Physicians to become a University president, the College takes pride in his success and submits herewith a synopsis of his brilliant career:

Born in Cathay, N. D., August 7, 1902, Dr. Allen holds five degrees from the University of Minnesota: B.S. (1924), M.A. (1925), M.B. and M.D. (1928), and Ph.D. (1934). His internship, 1926 to 1928, was spent at St. Mary's Hospital and Abbott Hospital, both of Minneapolis. He spent 18 months as a general practitioner at Minot, N. D., before going to Mayo Clinic (1930-1933) as a fellow in urology.

From July, 1934, until May, 1936, Dr. Allen served as associate dean in charge of graduate studies at the College of Physicians and Surgeons at Columbia University, and as associate director of the New York Postgraduate Medical School and Hospital. He was named Dean of Wayne University College of Medicine in May, 1936, where he served until September, 1939, when he went to Chicago as executive dean of the Chicago College of the University of Illinois. In 1941 he became Dean of the University's College of Medicine.

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The Passano Foundation Award of \$5000 was established in 1944 by the Williams and Wilkins Company, Medical Publishers, of Baltimore, to be awarded annually by the Foundation for the encouragement and advancement of medical research bearing promise of clinical application.

The medical profession on the Board of Directors of the Foundation is represented by Dr. Emil Novak, Associate in Gynecology, and Dr. Nicholson J. Eastman, Professor of Obstetrics, in the Johns Hopkins University Medical School, together with Dr. George W. Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington.

The 1946 recipient of the Passano Foundation Award is Dr. Ernest W. Goodpasture, Professor of Pathology and Dean of the School of Medicine of Vanderbilt University, Nashville, Tennessee, for his outstanding contributions to advancement of knowledge of the cell-parasite relationship in bacterial and virus infection and for his original development of the method for propagation of viruses in pure culture by inoculation of chick embryos which has immeasurably advanced our knowledge of virus diseases, as shown by the recent development of vaccines against several diseases common to both man and animal.

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SYNOPSIS OF GRADUATE TRAINING PROGRAM  
IN THE NAVY MEDICAL CORPS

The Professional Division of the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C., has recently released an outline of the graduate training program in the Navy Medical Corps, consisting of three general types:



- A. Intern Training
- B. Residency-Type Training
- C. Continuation and Special Courses

to increase the proficiency of medical officers and to improve the standards of medical practice in the Navy Medical Corps.

Approval of the U. S. Naval Hospitals for internship training is based upon standards of and action by the Council on Medical Education and Hospitals of the American Medical Association. Residency-type training in the Navy in medical and surgical specialties is also based upon the standards of this Council acting jointly with the American Boards of Certification, together with additional approval for graduate training in the surgical aspects promulgated by the American College of Surgeons. Nine naval hospitals have been designated as centers of residency-type training, located in:

Bethesda, Md.  
Chelsea, Mass.  
Great Lakes, Ill.  
Long Beach, Calif.  
Oakland, Calif.  
Philadelphia, Pa.  
San Diego, Calif.  
Seattle, Wash.  
St. Albans, N. Y.

These nine hospitals have been designated as teaching centers and each will have a consulting staff composed of certified specialists selected from outstanding officers of the Naval Medical Reserve Corps, inactive or resigned. Within Naval Hospitals there will be organized a Committee on Graduate Training.

In addition, the Bureau of Medicine and Surgery has established a special Reserve Consultants' Board to the Bureau. This Board is composed of reserve medical officers who are outstanding specialists in their respective fields and one of whom is a member of the Council on Medical Education of the American Medical Association.

An extensive program of training has been initiated in Naval Hospitals. Medical officers are encouraged to attend continuation and special postgraduate courses in the various specialties in addition to previously existing courses of instruction in lines of work peculiar to the Navy, such as aviation medicine, submarine medicine, preventive medicine, industrial medicine, medical statistics, research, island medical administration, tropical medicine, and epidemiology. A limited number of superior medical officers in the regular Navy Medical Corps may from time to time be assigned to civilian institutions for special training of one to two years duration.

Medical Officers desiring graduate training are encouraged to seek these opportunities, whether they propose merely to improve themselves as practitioners or to seek full qualification and recognition as specialists.

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The Surgeon General, Major General Norman T. Kirk, F.A.C.P., has announced availability of internships in U. S. Army Hospitals starting July 1, 1947, with the reserve commission of First Lieutenant in the Army Medical Corps at a salary of approximately \$3,400 annually. This year of clinical training will be of the conventional rotating type, and is recognized as such by the Council on Medical Education and Hospitals of the American Medical Association and the State Boards of Registration which require a clinical year of training prior to licensure.

Medical school graduates are assured of an interesting and profitable career of Army medicine if they elect to accept Regular Army commissions upon completion of the clinical internship in Army Hospitals. Selections will be based on scholastic attainment, physical fitness and aptitude for military service.

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Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., has endowed the Swanberg Medical Foundation of the Adams County Medical Society of Illinois for the benefit of the medical profession in general and of the Adams County Medical Society in particular. Dr. Swanberg in 1943 established an irrevocable trust whereby the income from this foundation may be used for a specific purpose that will bring public and professional honor and respect to the membership of the Adams County Medical Society, past, present and future. Dr. Swanberg's many interests center around postgraduate medical education, the Adams County Medical Society and the Mississippi Valley Medical Society of which organization he is a charter member, a life member and secretary. He is also a member of the Mississippi Valley Medical Editors' Association.

The present income from the Swanberg Medical Foundation now amounts to over \$600 annually.

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New York University College of Medicine and the Fourth Medical Division of Bellevue Hospital announced the Robert Trubek Fellowship in Rheumatic Disorders, a one-year, non-resident appointment open to graduate physicians with at least two years of previous training in internal medicine or its equivalent. The appointment is renewable for an additional year by mutual agreement. The Fellowship will combine supervised research and special clinical training in the rheumatic disorders under the direction of Dr. Otto Steinbrocker. Stipend \$2500 a year. (Candidates contemplating a two year tenure are preferred.)

Applicants should send their educational qualifications, accompanied by two letters of recommendation from senior physicians under whom work was done, to the Robert Trubek Fellowship Committee, Fourth Medical Division, Bellevue Hospital, 26th Street and First Avenue, New York 16, N. Y.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, presented a paper entitled "Psychosomatic Medicine and Diet Therapy" before the Pennsylvania Dietetic Association, Harrisburg, Pennsylvania, on May 2, 1946.

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The following Fellows of the College recently addressed the Fifty-Third Annual Session of the Oklahoma State Medical Association, Oklahoma City.

Dr. Wann Langston, F.A.C.P., Oklahoma City  
Dr. Herbert J. Rinkel, F.A.C.P., Kansas City  
Dr. Samuel R. Goodman, F.A.C.P., Tulsa  
Dr. E. Rankin Denny, F.A.C.P., Tulsa  
Dr. R. Q. Goodwin, F.A.C.P., Oklahoma City  
Dr. Homer A. Ruprecht, F.A.C.P., Tulsa  
Dr. Russell Haden, F.A.C.P., Cleveland, Ohio

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Dr. A. C. Cipollaro, F.A.C.P., has been appointed Assistant Director, Skin and Cancer Unit, New York Postgraduate Hospital, Columbia University.

Dr. William C. Menninger, F.A.C.P., Brigadier General, (MC), AUS, delivered the second Menas S. Gregory lecture of the New York University College of Medicine on April 26, 1946, at Bellevue Hospital, New York City. General Menninger discussed application of the lessons learned from military psychiatry to civilian psychiatry.

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Dr. Harold J. Harris, F.A.C.P., recently addressed the Maine Veterinary Medical Association in Portland, Maine.

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Dr. Albert Soiland, F.A.C.P., of Los Angeles, shortly before his recent death, established the Soiland Foundation to endow fellowships in cancer research in leading medical schools. Dr. Soiland endowed the Foundation with \$1,000,000 representing his lifetime savings over a period of 50 years.

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Dr. Olin Burnham Chamberlain, F.A.C.P., was recently retired from the Army as a Colonel and became the full time Professor of Neuropsychiatry at the Medical College of the State of South Carolina on April 1, 1946.

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Dr. Frederick G. Scovel, F.A.C.P., former Superintendent and Director of Medical Service of the Bachman-Hunter Hospital, Tsining, Shantung, China, is now located at the Presbyterian Mission in Huai Yuan, Anhwei, China.

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It was erroneously announced in a recent issue of this journal that Capt. Jerome T. Paul (Associate) of Chicago had been separated from the Army. Late word has been received to the effect that he is still on active duty.

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Dr. Henry Carl Rosenstiel (Associate), formerly of Freeport, Ill., has accepted an appointment as Internist at the Sheboygan (Wisconsin) Clinic.

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Dr. George W. Millett (Associate), formerly of San Francisco, has accepted an appointment as Clinical Director of the Thayer General Hospital, Nashville, Tenn., which is under the Veterans Administration.

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Dr. William D. Stroud, F.A.C.P., addressed the Medical Section of the New Jersey Medical Society recently.

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A special Regional Meeting of the College representing activities in Montana and Wyoming was held in Billings, Mont., on April 27. This Regional Meeting was in charge of Dr. Ernest D. Hitchcock, F.A.C.P., Great Falls, who is College Governor for Montana.

Included on the program were the following Fellows of the College:

Malcolm D. Winter, M.D., F.A.C.P., Miles City  
Maurice A. Shillington, M.D., F.A.C.P., Glendive  
Harold W. Gregg, M.D., F.A.C.P., Butte  
Ferdinand R. Schemm, M.D., F.A.C.P., Great Falls  
Allen R. Foss, M.D., F.A.C.P., Missoula  
Archie L. Gleason, M.D., F.A.C.P., Great Falls  
W. W. Arrasmith, M.D., F.A.C.P., Casper

Dr. Henry B. Kirkland, F.A.C.P., was recently separated from the Army of the United States with the rank of Lieutenant Colonel. Inadvertently, when his retirement was published in the Annals recently, his rank was given as Major. Dr. Kirkland has opened his offices at 370 Lexington Ave., New York City.

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The following Fellows of the College recently addressed the 10th Annual Post-graduate Institute of the Philadelphia County Medical Society held in Philadelphia, April 9-12:

Dr. John H. Willard, F.A.C.P., Philadelphia  
Dr. Garfield Duncan, F.A.C.P., Philadelphia  
Dr. Hobart A. Reimann, F.A.C.P., Philadelphia  
Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia  
Dr. Thomas M. McMillan, F.A.C.P., Philadelphia  
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia  
Dr. John Q. Griffith, Jr., F.A.C.P., Philadelphia  
Dr. Louis H. Clerf, F.A.C.P., Philadelphia  
Dr. Edward Rose, F.A.C.P., Philadelphia  
Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia  
Dr. H. L. Bockus, F.A.C.P., Philadelphia  
Dr. Harrison F. Flippin, F.A.C.P., Philadelphia  
Dr. Lowell Erf, F.A.C.P., Philadelphia  
Dr. David A. Cooper, F.A.C.P., Philadelphia

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At the meeting of the Texas State Heart Association in Galveston on May 6, 1946, the following officers were elected:

President: Dr. Robert M. Barton, F.A.C.P., Dallas  
Vice-President: Dr. Hatch W. Cummings (Associate), Houston  
Secretary-Treasurer: Dr. M. B. Whitten, F.A.C.P., Dallas

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The Indiana University School of Medicine and the Indiana State Board of Health sponsored a one day geriatrics institute on May 22. Dr. Leroy E. Burney (Associate), Indianapolis, state health commissioner, presided. The program included an address by Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., consultant in gerontology to the National Institute of Health.

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Dr. Samuel A. Levine, F.A.C.P., Boston, gave the third Walter Wile Hamburger Memorial Lecture of the Institute of Medicine of Chicago on May 24.

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Dr. Udo J. Wile, F.A.C.P., Ann Arbor, was recently made "Commander of the Order of Public Health," a decoration awarded by the French minister of health to Dr. Wile for instituting a venereal disease program in France.

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Dr. Paul G. Bowman, F.A.C.P., and Dr. Daniel W. Wheeler, F.A.C.P., both of Duluth, Minn., were elected president and president-elect, respectively, of the St. Louis County Medical Society of Minnesota.

Dr. Robert H. Williams (Associate), Boston, gave the spring lecture of Alpha Omega Alpha at Syracuse University College of Medicine on March 7.

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Dr. John S. LaDue (Associate), New York, and Dr. Robert H. Bayley, F.A.C.P., Oklahoma City, have been elected, respectively, chairman of the eastern and southern sections of the American Federation for Clinical Research. Dr. Richard H. Lyons, F.A.C.P., Ann Arbor, Mich., is secretary-treasurer of this organization.

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Dr. David M. Caldwell (Associate), Santa Barbara, Calif., was recently appointed Medical Director of the Tuberculosis Division of the Santa Barbara General Hospital. He restricts his work to diseases of the chest.

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Dr. Elaine Ralli, F.A.C.P., of New York City, was recently elected president of the Women's Medical Association of New York City.

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Dr. John K. Deegan, F.A.C.P., of Newport, Rhode Island, has returned from military service and accepted an appointment in the new Department of Medicine and Surgery of the Veterans Administration. He has assumed the duties of Clinical Director of the Veterans Tuberculosis Hospital at Castle Point, N. Y. Before his entrance on active duty with the Army, Dr. Deegan was associated with the New York State Department of Health as Superintendent and Medical Director, Biggs Memorial Hospital, Ithaca, New York. He formerly was Clinical Instructor in Medicine, Yale University Medical School. He is a Fellow of the American College of Physicians and a member of the American Public Health Association, the American Medical Association and the American Trudeau Society.

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Dr. Christopher N. Parnall, Jr., F.A.C.P., who has just returned from military service, has accepted an appointment in the new Department of Medicine and Surgery of the Veterans Administration and has reported for duty at the Veterans Tuberculosis Hospital at Oteen, North Carolina, as Chief, Tuberculosis Section.

Dr. Parnall had extended service with the Army in World War II, first at Walter Reed General Hospital and the Office of the Surgeon General in Washington and then in England and France with the 19th General Hospital. He formerly was Instructor in Medicine at the University of Michigan School of Medicine and the Louisiana State University Medical School.

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Dr. Benjamin L. Brock, F.A.C.P., of Waverly Hills, Kentucky, has resigned as Medical Director of the Waverly Hills Sanatorium and as Tuberculosis Controller of the city of Louisville and Jefferson County, Kentucky, to accept a position with the Veterans Administration as Clinical Director of its largest tuberculosis hospital at Oteen, North Carolina. Dr. Brock has been Associate Professor of Medicine at the University of Louisville School of Medicine since 1938 and has made a number of contributions to the literature on tuberculosis. He is a veteran of the World War; Fellow of the American College of Physicians; Fellow of the American College of Chest Physicians and a member of the American Trudeau Society and the American Medical Association.

## GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged.

David L. Beers (Associate), Warren, Ohio—1 reprint.  
 J. Edward Berk, F.A.C.P., Philadelphia, Pa.—1 reprint.  
 Guy W. Carlson, F.A.C.P., Appleton, Wis.—1 reprint.  
 G. H. Faget, F.A.C.P., Carville, La.—2 reprints.  
 Lawrence W. Holden (Associate), Boulder, Colo.—1 reprint.  
 Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint.  
 Hilton S. Read, F.A.C.P., Atlantic City, N. J.—5 reprints.  
 Sidney Scherlis (Associate), Staunton, Va.—1 reprint.  
 C. C. Shaw, F.A.C.P., Philadelphia, Pa.—1 reprint.  
 Norman R. Shulack (Associate), Brooklyn, N. Y.—1 reprint.  
 C. B. Whims (Associate), Atlantic City, N. J.—1 reprint.  
 Charles Windwer, F.A.C.P., Brooklyn, N. Y.—1 reprint.  
 Edwin E. Ziegler, F.A.C.P., Lancaster, Pa.—1 reprint.

The College acknowledges with thanks to the author, Dr. Robert K. Maddock (Associate), Brooklyn, N. Y., a copy of his book entitled "United States Maritime Service Hospital Corps School Manual," which has been added to the College library; also, to Dr. F. B. Peck, F.A.C.P., Indianapolis, a bound copy of "Diabetes Abstracts, Vol. 4, 1945."

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 RETIREMENTS FROM SERVICE

Since the last publication of this Journal, the following members of the College have been reported retired or on terminal leave (to May 13, 1946, inclusive).

Benjamin I. Ashe, New York, N. Y. (Col., MC, AUS)  
 Wardner D. Ayer, Syracuse, N. Y. (Col., MC, AUS)

Andrew M. Babey, Brooklyn, N. Y. (Lt. Comdr., MC, USNR)

Horace M. Banks, Indianapolis, Ind. (Lt. Col., MC, AUS)

Sim F. Beam, St. Louis, Mo. (Col., MC, AUS)

George O. Bell, Waban, Mass. (Major, MC, AUS)

Murray Benson, New York, N. Y. (Major, MC, AUS)

Edmund H. Berger, Portland, Ore. (Comdr., MC, USNR)

William L. Bettison, Grand Rapids, Mich. (Major, MC, AUS)

Samuel Blackwell, Memphis, Tenn. (Major, MC, AUS)

Osborne A. Brines, Detroit, Mich. (Capt., MC, USNR)

Hugh R. Butt, Rochester, Minn. (Lt. Comdr., MC, USNR)

Hayes W. Caldwell, Rochester, Minn. (Capt., MC, AUS)

John D. Call, Rochester, Minn. (Lt., MC, USNR)

Donald C. Campbell, Rochester, Minn. (Major, MC, AUS)

Horace B. Cates, Los Angeles, Calif. (Major, MC, AUS)

Olin B. Chamberlain, Charleston, S. C. (Col., MC, AUS)

Donald T. Chamberlin, Boston, Mass. (Lt. Col., MC, AUS)

T. Sterling Claiborne, Atlanta, Ga. (Lt. Col., MC, AUS)

James H. Closson, Philadelphia, Pa. (Comdr., MC, USNR)

Aloysius J. B. Connolly, Washington, D. C. (Lt. Comdr., MC, USNR)

Marvin B. Corlette, Pasadena, Calif. (Major, MC, AUS)

Einar R. Daniels, Milwaukee, Wis. (Lt. Col., MC, AUS)  
 Alva D. Daughton, Washington, D. C. (Col., MC, AUS)  
 Karl L. Dickens, Martinsville, Ind. (Lt., MC, USNR)  
 Ralph L. Drake, Wichita, Kan. (Lt. Col., MC, AUS)  
 Charles L. Dunham, Chicago, Ill. (Capt., MC, AUS)  
 Ralph E. Durkee, Jr., Hartford, Conn. (Surgeon, USPHS(R))

Nathan H. Einhorn, Philadelphia, Pa. (Col., MC, AUS)  
 Eugene A. Eisner, New York, N. Y. (Lt. Comdr., MC, USNR)  
 Louis S. Faust, Denver, Colo. (Major, MC, AUS)  
 John W. Ferree, Indianapolis, Ind. (Comdr., MC, USNR)  
 Rexford W. Finegan, New York, N. Y. (Lt. Col., MC, AUS)  
 Alfred Fleishman, St. Louis, Mo. (Major, MC, AUS)  
 Stuart O. Foster, Washington, D. C. (Col., MC, AUS)

Stuart N. Gardner, Salem, Mass. (Capt., MC, USNR)  
 Russell A. Garman, Jeannette, Pa. (Lt. Comdr., MC, USNR)  
 James T. Gilbert, Jr., Bowling Green, Ky. (Major, MC, AUS)  
 Stanley M. Goldhamer, Ann Arbor, Mich. (Lt. Col., MC, AUS)  
 Edgar S. Gordon, Madison, Wis. (Lt. Col., MC, AUS)  
 Ben Ely Grant, Los Angeles, Calif. (Col., MC, AUS)  
 John H. Greist, Indianapolis, Ind. (Col., MC, AUS)  
 John E. Greutter, Little Rock, Ark. (Major, MC, AUS)

Phillip Hallock, Minneapolis, Minn. (Lt. Col., MC, AUS)  
 Harry Halprin, Caldwell, N. J. (Comdr., MC, USNR)  
 Thomas H. Ham, Boston, Mass. (Lt. Col., MC, AUS)  
 J. Watson Harmeier, Pittsburgh, Pa. (Lt. Col., MC, AUS)  
 George H. Houck, Los Angeles, Calif. (Col., MC, AUS)  
 William L. Howell, Fort Worth, Tex. (Major, MC, AUS)

Alfred P. Ingegno, Brooklyn, N. Y. (Lt. Col., MC, AUS)

Mennasch Kalkstein, New York, N. Y. (Lt. Col., MC, AUS)  
 Murrel H. Kaplan, New Orleans, La. (Major, MC, AUS)  
 Bruce D. Kenamore, St. Louis, Mo. (Major, MC, AUS)  
 John J. Keveney, Philadelphia, Pa. (Major, MC, AUS)  
 Hugh E. Kiene, Providence, R. I. (Lt. Col., MC, AUS)  
 Robert C. Kimbrough, Ann Arbor, Mich. (Lt. Col., MC, AUS)  
 Donald S. King, Brookline, Mass. (Col., MC, AUS)  
 John T. King, Baltimore, Md. (Col., MC, AUS)  
 Joseph B. Kirsner, Chicago, Ill. (Major, MC, AUS)  
 Arthur Klein, Richmond, Va. (Lt., MC, AUS)  
 Isadore J. Kwitny, Indianapolis, Ind. (Lt. Col., MC, AUS)

Michael Lake, New York, N. Y. (Capt., MC, USNR)  
 Herman Lande, New York, N. Y. (Col., MC, AUS)  
 Lee H. Leger, Kansas City, Mo. (Lt. Col., MC, AUS)  
 Louis E. Lieder, Cleveland, Ohio (Lt. Col., MC, AUS)  
 Eugene J. Lippschutz, Buffalo, N. Y. (Comdr., MC, USNR)  
 George Lorenz, Jr., Philadelphia, Pa. (Comdr., MC, USNR)

Frank R. Maddison, Tacoma, Wash. (Major, MC, AUS)  
 Frank X. Marino, New Orleans, La. (Capt., MC, AUS)  
 Norval M. Marr, St. Petersburg, Fla. (Capt., MC, USNR)  
 John F. McManus, West Newton, Mass. (Major, MC, AUS)

J. Stuart McQuiston, Cedar Rapids, Iowa (Lt. Col., MC, AUS)  
Lodwick S. Meriwether, Jackson, Miss. (Lt. Col., MC, AUS)  
Raymond E. Miller, New York, N. Y. (Lt. Comdr., MC, USNR)  
Earl L. Mills, Wichita, Kan. (Lt. Col., MC, AUS)  
John H. Mills, Spokane, Wash. (Lt. Col., MC, AUS)  
A. Mogabgab, New Orleans, La. (Col., MC, AUS)  
Hugh Montgomery, Philadelphia, Pa. (Comdr., MC, USNR)  
Bert E. Mulvey, Oklahoma City, Okla. (Lt. Col., MC, AUS)  
William N. Myhre, Spokane, Wash. (Lt., MC, USNR)

J. Ernest Nadler, Jackson Heights, N. Y. (Comdr., MC, USNR)  
J. Marshall Neely, Lincoln, Nebr. (Lt. Comdr., MC, USNR)

Adolph T. Ogaard, New Orleans, La. (Major, MC, AUS)

Joseph F. Painton, Buffalo, N. Y. (Lt. Col., MC, AUS)  
Sol S. Parent, Newark, N. J. (Lt. Col., MC, AUS)  
Hubert McKibban Parker, Kansas City, Mo. (Lt. Col., MC, AUS)  
Martin Patmos, Kalamazoo, Mich. (Lt. Col., MC, AUS)  
George W. Pedigo, Jr. Louisville, Ky. (Capt., MC, AUS)  
Kenneth Phillips, Miami, Fla. (Comdr., MC, USNR)  
Carlos A. Pons, Asbury Park, N. J. (Lt. Col., MC, AUS)  
Joseph Post, New York, N. Y. (Major, MC, AUS)  
Vernon E. Powell, Atlanta, Ga. (Lt. Col., MC, AUS)  
William L. Powers, Wichita Falls, Tex. (Comdr., MC, USNR)

Earl B. Ray, Bellflower, Calif. (Col., MC, AUS)  
Cornelius P. Rhoads, New York, N. Y. (Col., MC, AUS)  
Charles J. Roberts, Enid, Okla. (Lt. Col., MC, AUS)  
Bernard D. Rosenak, Indianapolis, Ind. (Capt., MC, AUS)  
Donald H. Root, Quincy, Ill. (Major, MC, AUS)  
James W. H. Rouse, Fort Worth, Tex. (Col., MC, AUS)

Walter L. Schafer, Wheeling, W. Va. (Comdr., MC, USNR)  
John C. Schlappi, San Diego, Calif. (Comdr., MC, USNR)  
Curt P. Schneider, Detroit, Mich. (Comdr., MC, USNR)  
Thornton Scott, Lexington, Ky. (Comdr., MC, USNR)  
Charles L. Short, Boston, Mass. (Lt. Col., MC, AUS)  
Solomon Silver, New York, N. Y. (Lt. Col., MC, AUS)  
W. Walter Sittler, Chicago, Ill. (Comdr., MC, USNR)  
Hyman A. Slesinger, Windber, Pa. (Major, MC, AUS)  
Frank E. Smith, Jr., New York, N. Y. (Lt. Comdr., MC, USNR)  
Robert H. Southcombe, Spokane, Wash. (Comdr., MC, USNR)  
Thomas N. Spessard, Norfolk, Va. (Capt., MC, USNR)  
Arthur S. Strauss, White Plains, N. Y. (Lt. Col., MC, AUS)  
George W. Stuppy, Chicago, Ill. (Lt. Col., MC, AUS)

Milo K. Tedstrom, Santa Ana, Calif. (Lt. Col., MC, AUS)  
Ivan Thompson, Ogden, Utah (Lt. Comdr., MC, USNR)  
Wilmot C. Townsend, West Hartford, Conn. (Col., MC, AUS)  
T. Lloyd Tyson, New York, N. Y. (Major, MC, AUS)

Neville T. Ussher, Santa Barbara, Calif. (Lt. Col., MC, AUS)

Joseph B. Vander Veer, Philadelphia, Pa. (Col., MC, AUS)  
Louis D. Vaughn, Rochester, Minn. (Major, MC, AUS)  
Walter L. Voegtlin, Seattle, Wash. (Comdr., MC, USNR)



Douglass W. Walker, New Haven, Conn. (Lt. Col., MC, AUS)  
 James A. Walsh, Peoria, Ill. (Major, MC, AUS)  
 J. Harold Watkins, Montgomery, Ala. (Col., MC, AUS)  
 Guy W. Wells, Providence, R. I. (Col., MC, AUS)  
 Daniel W. Wheeler, Duluth, Minn. (Capt., MC, USNR)  
 Lee Williamson, Terrell, Tex. (Capt., MC, AUS)  
 Walter H. Wilson, Greenville, N. C. (Major, MC, AUS)  
 R. Hugh Wood, Atlanta, Ga. (Col., MC, AUS)  
 Philip Work, Denver, Colo. (Col., MC, AUS)  
 Thomas L. Worsley, Jr., Baltimore, Md. (Capt., MC, AUS)

The following physicians, having fulfilled all requirements, professional and personal, were elected to the respective classes of membership indicated by the Board of Regents at Philadelphia, May 12, 1946.

#### ELECTED TO FELLOWSHIP

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 Walter Francis Berberich, (MC), USN, Annapolis, Md.  
 Philip Bernard Bleecker, Memphis, Tenn.  
 Benjamin Burroughs Bushong, Ann Arbor, Mich.

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 Herbert Chasis, New York, N. Y.  
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 Oliver Spurgeon English, Philadelphia, Pa.

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 Arthur Allyn Fischl, Astoria, L. I., N. Y.  
 Harold Freed, Dallas, Tex.

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 Howard Eugene Heyer, Dallas, Tex.  
 Edwin Frederick Hirsch, Chicago, Ill.  
 William Maxwell Hitzig, New York, N. Y.  
 Axel Magnus Hjort, Scarsdale, N. Y.

William Knowlton Ishmael, Oklahoma City, Okla.

Victor Einar Johnson, Chicago, Ill.

Edwin Pratt Jordan, Chicago, Ill.

Murrel Herman Kaplan, New Orleans, La.

Paul Edmund Keller, (MC), USA, Fort Douglas, Utah

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Max Harry Rosenblum, Steubenville, Ohio

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Rudolf Schindler, Los Angeles, Calif.

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William Stein, New Brunswick, N. J.

James Minott Stickney, Rochester, Minn.

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Gilman Rackley Tyler, Richmond, Va.

Arie Cornelius van Ravenswaay, Boonville, Mo.

Donald Jasper Wilson, Omaha, Nebr.

Michael Gershon Wohl, Philadelphia, Pa.

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Charles Edward Anderson, Jr., Shreveport, La.

Horace Alfred Anderson, Independence, Kan.

Walter Lyman Anderson, Detroit, Mich.

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 Gordon Irving Bell, Edmonton, Alta., Can.  
 Charles Edward Bender, Seattle, Wash.  
 Eugene Sydney Bereston, Baltimore, Md.  
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 Paul William Berney, Columbus, Nebr.  
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Elwyn Lindley Heller, Pittsburgh, Pa.  
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Joseph Spurgeon Hiatt, Jr., Sanatorium, N. C.  
Richards Holmes Hoffman, Bellefonte, Pa.  
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Henry Horn, New York, N. Y.  
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Ralph Henry Huff, Tacoma, Wash.

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 Milo George Meyer, Marshalltown, Iowa  
 Henry Miller, Providence, R. I.  
 F. Stanley Morest, Kansas City, Mo.  
 Philip Morgenstern, Huntsville, Ala.  
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 Alvin Beckham Mullen, Waverly Hills, Ky.

Paul Van Dyne Newland, Clifton Springs, N. Y.  
 William Strange Norton, II, New York, N. Y.

Theodore Wright Oppel, New York, N. Y.

Margaret Virginia Palmer, Easton, Md.  
 Russell Alfred Palmer, Vancouver, B. C., Can.  
 Charles Stehman Pennypacker, Ardmore, Pa.  
 George William Perdue, Houston, Tex.  
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 Alberto Prieto, New Orleans, La.  
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 Wellford Claiborne Reed, Richmond, Va.  
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 Seymour Harold Rinzler, New York, N. Y.  
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 Arthur Merriam Rogers, Philadelphia, Pa.  
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 Ludwig Theodore Rosenthal, Philadelphia, Pa.  
 Paul Selbert Ross, Columbus, Ohio  
 Norman Oliver Rothermich, Columbus, Ohio

Carlos F. Sacasa, Pasadena, Calif.  
 Joseph Francis Sadusk, Jr., New Haven, Conn.  
 Stuart Sanger, Tucson, Ariz.  
 Sanford Sarney, Brooklyn, N. Y.  
 John Joyce Sayem, Philadelphia, Pa.  
 Samuel Jacob Schneierson, New York, N. Y.  
 William Schulze, Greenville, S. C.

Steven Otto Schwartz, Chicago, Ill.  
David Schwimmer, New York, N. Y.  
Joseph Eckles Scott, Portland, Ore.  
Leonard Shapiro, Brooklyn, N. Y.  
Moses Samuel Shiling, Baltimore, Md.  
Bliss Calcliffe Shrapnel, Ancon, C. Z.  
Harrison Johnston Shull, Nashville, Tenn.  
Sheppard Siegal, New York, N. Y.  
Martin Louis Singewald, Baltimore, Md.  
Norman G. Sloane, Philadelphia, Pa.  
Carroll Collom Smith, Oklahoma City, Okla.  
Herman Joseph Smith, Des Moines, Iowa  
R. Eloise Smith, Clifton Springs, N. Y.  
Warren Braman Smith, Danville, Ill.  
Sydney Solomon, Bronx, N. Y.  
Samuel Herman Spitz, Brooklyn, N. Y.  
Harold Ervin Stadler, Indianapolis, Ind.  
Walker Stamps, Jacksonville, Fla.  
Harold Stevens, Washington, D. C.  
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Robert William Vines, Denver, Colo.  
Christopher G. Vournas, St. Louis, Mo.  
  
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John Michael Wagner, Clarks Summit, Pa.  
Eugene Louis B. Walsh, Huntington, W. Va.  
Joseph Edward Walther, Jr., Indianapolis, Ind.  
Lawrence Wechsler, Pittsburgh, Pa.  
Hyam Arne Weiner, Baltimore, Md.  
Allen Abraham Welkind, Newark, N. J.  
John Ovenstone Westwater, Los Angeles, Calif.  
Robert Harvey Whiting, Edmonton, Alta., Can.  
Arnold Harry Widerman, Philadelphia, Pa.  
Ray David Williams, St. Louis, Mo.  
Sigmund Samuel Winton, Chicago, Ill.  
Victor Felsenthal Woolf, New York, N. Y.  
Duward Olera Wright, Fort Payne, Ala.  
Carl Iglauer Wyler, Cincinnati, Ohio  
  
Andrew Yeomans, Brookline, Mass.  
MacLean Kenneth Young, Edmonton, Alta., Can.  
Richard Wallace Young, Baton Rouge, La.  
  
Kurt Zinner, Wellsville, N. Y.

*OBITUARIES*

## DR. CLEMENT RUSSELL JONES

Dr. Clement Russell Jones, F.A.C.P., died suddenly at his home in Pittsburgh, Pa., on September 3, 1945.

Born in 1871, he attended the Columbus Medical College where he received his degree of Doctor of Medicine in 1892.

For many years, Dr. Jones was Professor of the Principles of Medicine, University of Pittsburgh School of Dentistry, and Assistant Professor of Medicine, University of Pittsburgh School of Medicine. He was an active member of the Medical Staff of the Mercy and Presbyterian Hospitals and of the Falk Clinic of the University of Pittsburgh. He held the post of attending chief of medicine at the Pittsburgh City Home and Hospitals (Mayview).

Dr. Jones was an Ex-Treasurer and Ex-Regent of the American College of Physicians. He became a Fellow in 1916.

## DR. HOWARD JONES

Dr. Howard Jones, A.B., A.M., M.D., of Circleville, Ohio, was born August 24, 1853. He was graduated from the Medical College of Ohio in 1876. He was intensely interested in scientific medicine and pursued a post-graduate course at the College of Physicians and Surgeons, Columbia University. He enjoyed a Professorship at Columbus Medical College where he taught and lectured on Physiology. He also lectured on Physiology at Kenyon College. He was a member of the staff of the Berger Hospital for a number of years. He was also President and Vice-President of the Piqua County Medical Society.

He was extremely interested in bird life and was the author of "Nests and Eggs of Birds of Ohio."

He was made an Associate of the American College of Physicians in 1924 by virtue of his former membership in the American Congress of Internal Medicine. He died of natural causes on December 12, 1945, at the age of 92.

A. B. BROWER, M.D.; F.A.C.P.

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